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L2	hydrogen adj peroxide	93958	L2
L1	steriliz$ same chamber same (vacu$ or pressure) same plasma	270	L1

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L3: Entry 33 of 147 File: USPT Sep 30, 2003

DOCUMENT-IDENTIFIER: US 6627150 B1
TITLE: Method of sterilizing an article and certifying the article as sterile

Abstract Text (1):
The present invention relates to a process for sterilization of medical instruments by concentrating a sterilant such as hydrogen peroxide inside of a sterilizer and sterilizing articles therewith. This concentrating process is monitored by determining the concentrations of water and peroxide in the chamber.

Brief Summary Text (5):
Sterilization using liquid hydrogen peroxide solution has been found to require high concentrations of sterilant, extended exposure time and/or elevated temperatures. However, sterilization using hydrogen peroxide vapor has been shown to have some advantages over other chemical sterilization processes (see, e.g., U.S. Pat. Nos. 4,169,123 and 4,169,124, each of which issued Sep. 25, 1979, which are entitled respectively, "Hydrogen Peroxide Vapor Sterilization Method" and "Cold Gas Sterilization Process" and which are incorporated herein by reference).

Brief Summary Text (6):
The combination of hydrogen peroxide with a plasma provides certain additional advantages, as disclosed in U.S. Pat. No. 4,643,876 issued Feb. 17, 1987 and entitled, "Hydrogen Peroxide Plasma Sterilization System" which is incorporated herein by reference. Commercially available sterilization devices, such as the STERRAD.RTM. sterilization systems sold by Advanced Sterilization Systems division of Ethicon, Inc. automate the process of injecting a solution of hydrogen peroxide into a sterilization chamber, vaporizing the solution to provide a hydrogen peroxide vapor, contacting articles to be sterilized with the vapor, and exciting the vapor into the plasma stage. The hydrogen peroxide for each sterilization cycle is shipped to the location of the sterilization system, generally by air or ground transportation.

Brief Summary Text (7):
Preferably, as in the case with the STERRAD.RTM. brand systems, pre-measured amounts of a hydrogen peroxide and water solution are provided in sealed enclosure, such as a capsule inside of a cassette housing which can be automatically opened by the system to reduce contact between the system user and the hydrogen peroxide solution. Such cassettes are described more fully in U.S. Pat. No. 4,817,800 issued Apr. 4, 1989 entitled, "Fluid Injection System Cassette and Fluid Packaging Methods" and U.S. Pat. No. 4,899,519 issued Feb. 13, 1990 with the same title, each of which are incorporated herein by reference.

Brief Summary Text (8):
The sterilization of articles containing diffusion-restricted areas, such as long narrow lumens, presents a special challenge. Methods that use hydrogen peroxide vapor that has been generated from an aqueous solution of hydrogen peroxide have certain disadvantages. One disadvantage is that because water has a higher vapor pressure than hydrogen peroxide, it will vaporize faster. Another disadvantage is that because of its lower molecular weight, water will diffuse faster than hydrogen peroxide in the vapor state. Because of these physical properties, when an aqueous solution of hydrogen peroxide is vaporized in the area surrounding the items to be sterilized, the water reaches the items first and in higher concentration. The water vapor more quickly diffuses into and thus inhibits penetration of hydrogen peroxide vapor into diffusion-restricted areas, such as small crevices and lone narrow lumens. Simply employing a more concentrated solution of hydrogen peroxide fails to adequately address the problem due to the difficulty in handling highly concentrated hydrogen peroxide solutions. Transportation of such solutions can be particularly difficult. In general, such solutions are limited to concentrations of less than 60% hydrogen peroxide,

however, regulations and the like regarding such concentrations may of course be modified in the future. In any event, shipping and handling of highly concentrated solutions remains impractical.

Brief Summary Text (9):
U.S. Pat. No. 4,952,370 issued Aug. 28, 1990 and entitled "Hydrogen Peroxide Sterilization Method" and incorporated herein by reference discloses a sterilization process in which aqueous hydrogen peroxide vapor is first condensed on the article to be sterilized, followed by application of a vacuum to the sterilization chamber to remove the water and hydrogen peroxide from the article. This method is suitable for surface sterilization, but not for sterilization of diffusion-restricted areas such as long narrow lumens because it depends on the diffusion of hydrogen peroxide vapor into the lumen to effect sterilization.

Brief Summary Text (10):
U.S. Pat. No. 4,943,414 issued Jul. 24, 1990 and entitled "Method for Vapor Sterilization of Articles Having Lumens" discloses a process in which a vessel containing a small amount of a vaporizable liquid sterilant solution is attached to a lumen, and the sterilant vaporizes and flows directly into the lumen of the article as the pressure is reduced during the sterilization cycle. This system has the advantage that the water and hydrogen peroxide vapor are pulled through the lumen by the existing pressure differential, increasing the sterilization rate for lumens, but has the disadvantage that the vessel needs to be attached to each lumen to be sterilized.

Brief Summary Text (12):
U.S. Pat. No. 4,744,951 issued May 17, 1988 to Cummings and entitled "Vaporization met,hod to Enhance Sterilant Penetration" attempts to address this problem by providing a separate prechamber connected to the sterilization chamber. Hydrogen peroxide is first admitted to the prechamber where it is concentrated in a distillation procedure employing the differing vapor pressures of hydrogen peroxide and water. Water's higher vapor pressure allows one to select a vaporization pressure that selectively vaporizes water from a hydrogen peroxide solution, thus concentrating the solution. Cummings pumps air out of the prechamber and lowers its pressure to a level at which the water preferentially vaporizes from the hydrogen peroxide solution. The pump that is evacuating the prechamber draws out the water vapor thus released from solution to concentrate the remaining solution. To prevent the water vapor from traveling into the narrow spaces such as endoscope lumens, Cummings carries out the concentration process in the prechamber which is physically isolated from the main chamber. This adds complexity by requiring additional chambers, pumps and valves.

Brief Summary Text (13):
Those of skill in the art would not think to employ such a concentration process in the same chamber as the sterilization occurs. Such a process first draws the water out of solution and it would have been thought that this water vapor would simply enter and thus occlude the narrow lumens, thereby inhibiting the later diffusion of hydrogen peroxide, no matter how concentrated, into those lumens. However, the present inventors have surprisingly found that concentrating the hydrogen peroxide vapor within the sterilization chamber greatly increases the ability to sterilize long narrow lumens over the conventional process.

Brief Summary Text (14):
An additional advantage of the ability to concentrate the hydrogen peroxide is the ability to accurately predict the outcome of a sterilization cycle. Normally, some form of biological indicator containing a test microorganism is included with a load of instruments to be sterilized and the load is not certified as being sterile and ready for use without first checking to see whether the microorganisms in the biological indicator are killed. Applicants have surprisingly found that by sufficiently concentrating the hydrogen peroxide and monitoring that the concentration is achieved that the sterilization process is so predictable as to be able to release a load as sterilized without the need for a further biological indicator reading, i.e. parametric release.

Brief Summary Text (16):
The present invention comprises a method of sterilizing, and certifying as sterile, an article. It includes the steps of: a) placing the article into a sterilizer; b) introducing hydrogen peroxide and water into the sterilizer c) vaporizing the hydrogen peroxide and water to form a vapor comprising hydrogen peroxide and water; d) determining the concentration of hydrogen peroxide in the vapor; e) determining the concentration of water in the vapor; f) selectively drawing water vapor from the

sterilizer to increase the ratio of hydrogen peroxide to water in the sterilizer; g) repeating steps c)-f) until the ratio of hydrogen peroxide to water is at a desired level; and h) furnishing the vaporized hydrogen peroxide to the article for a sufficient time to effect sterilization thereof and then certifying the sterility of the article based upon achieving the desired level.

Brief Summary Text (17):
Preferably, such desired level is chosen from the group consisting of: i) attaining a ratio of hydrogen peroxide to water of at least 0.1 to 1 by weight, ii) attaining a ratio of hydrogen peroxide to water in the vapor which is at least two times higher than the ratio of hydrogen peroxide to water which is introduced into the sterilizer in step b), iii) attaining a concentration of hydrogen peroxide and water of at least 60% by weight of hydrogen peroxide, and iv) attaining a hydrogen peroxide concentration of at least 0.45 mg/L.

Brief Summary Text (18):
The sterilizer may comprise a diffusion-restricted area. The sterilizer may comprises a chamber and an enclosure, with the enclosure in fluid communication with the chamber. The hydrogen peroxide and water are introduced into the sterilizer via the enclosure. The enclosure may also comprise a diffusion restricted area.

Brief Summary Text (19):
In one aspect of the invention the ratio of hydrogen peroxide to water introduced into the sterilizer is less than 0.1 to 1 by weight. Preferably, the sterilizer is evacuated to a pressure below the atmospheric pressure, more preferably to a pressure below the vapor pressure of the hydrogen peroxide and water in solution.

Brief Summary Text (20):
Preferably, the concentration of hydrogen peroxide occurs in solution so that after the ratio of hydrogen peroxide to water is at the desired level a portion of the hydrogen peroxide remains in liquid form and is then vaporized.

Brief Summary Text (22):
Preferably, the temperature of unvaporized hydrogen peroxide and water in the sterilizer is monitored to more accurately control the vaporizing process.

Brief Summary Text (24):
In one aspect of the invention the hydrogen peroxide vapor is furnished to the article for a period of at least 15 minutes, or alternatively for at least 30 minutes.

Drawing Description Text (2):
FIG. 1 is a schematic diagram of a chamber and accessories suitable for use in the hydrogen peroxide sterilization process of the invention.

Drawing Description Text (3):
FIG. 2 is a schematic diagram of a chamber, pump and throttle valve for use in the hydrogen peroxide sterilization process of the invention.

Detailed Description Text (2):
Sterilizing the inside of lumened devices has always posed a challenge to sterilization systems. Co-pending U.S. application No. 08/628,965, and its related issued U.S. Pat. No. 5,980,825 issued Nov. 9, 1999, the entire contents of which are hereby incorporated by reference, disclose a method of hydrogen peroxide vapor sterilization of diffusion-restricted environments, such as long narrow lumens, at pressures less than the vapor pressure of hydrogen peroxide by pretreating the article to be sterilized with a dilute solution of hydrogen peroxide prior to exposure to a vacuum. U.S. Pat. No. 5,851,485, issued Dec. 22, 1998 incorporated herein by reference, controls the pumpdown rate.

Detailed Description Text (4):
Hydrogen peroxide can be introduced into the system in any fashion. In one embodiment, a dilute, aqueous solution of hydrogen peroxide is placed in wells 8 as shown in FIG. 1. The aqueous solution of hydrogen peroxide can also be placed within the lumen of long narrow objects to be sterilized. As the pressure in the sterilization chamber 2 is reduced, the hydrogen peroxide vaporizes and contacts the surface to be sterilized (i.e., colonoscope 10 in FIG. 1) which is placed on metal grid 12 which rests on tray 14. In a preferred embodiment, the tray can be configured with a plurality of wells designed to retain a known volume of liquid sterilant. In one embodiment, the volume of sterilization chamber 2 is about 18.5 liters and its dimensions are about 22"(55.9

cm).times.4.25"(10.8 cm).times.12"(30.5 cm).

Detailed Description Text (5):
FIG. 3 illustrates a parallel two-valve arrangement for use in the sterilization process of the invention. In this embodiment, the chamber 2 is in fluid communication with the pump 6 via valves 16 and 18. Valve 16 mediates the initial rapid evacuation, the first step of a two step evacuation process. Valve 18 mediates slow evacuation, the second step of the process, which ensures maximal contact of the article to be sterilized with the vaporized aqueous hydrogen peroxide. The pumpdown rate can be controlled by the pumping speed and/or the percent opening of the valve. Either valve can be used to maintain the pressure. In practice, controlling the process so that all of the water evaporates before any of the hydrogen peroxide evaporates is very difficult, yet the preferential evaporation and elimination of water vapor from the system effectively concentrates the hydrogen peroxide therein without the attendant complexity of shipping and handling concentrated hydrogen peroxide solutions prior to vaporization.

Detailed Description Text (8):
Regardless of which configuration is used, hydrogen peroxide can be introduced into the chamber as a liquid. In one preferred embodiment, hydrogen peroxide is introduced as a vapor and the chamber parameters are changed so that the vapor condenses as a liquid on the surface of interior of an article to be sterilized. Such changes include increasing the pressure.

Detailed Description Text (9):
The aqueous solutions of hydrogen peroxide can be relatively dilute, e.g. as low as 1-6% peroxide by weight, since sterilization is not achieved through contact with the hydrogen peroxide solution, but rather is achieved at low temperatures (preferably 15-80.degree. C., more preferably 20-60.degree. C., still more preferably 40-55.degree. C.) and in short periods of time (preferably less than one hour and more preferably less than one-half hour) upon exposure to hydrogen peroxide under vacuum. The method of the present invention is particularly effective with articles having inaccessible or hard-to-reach places. Such articles include long, narrow lumens, hinges and other articles having spaces where diffusion of vapors is restricted. Although hydrogen peroxide is used in the examples described herein, the use of other liquid sterilants which have vapor pressures lower than the vapor pressure of the solvent in which they are provided are also contemplated. Such sterilants include, for example, aqueous peracetic acid solution and aqueous glutaraldehyde solution.

Detailed Description Text (13):
For certain substrates being sterilized, such as nylon or polyurethane, excess hydrogen peroxide in the system may leave a residual which is difficult to be removed. In order to avoid an excess residual, the vapor concentration of hydrogen peroxide is preferably kept below 30 mg/l, more preferably less than 20 mg/l, and more preferably still less than 15 mg/l. If higher vapor concentrations of hydrogen peroxide are desired, excess residual can be removed using a gas plasma. When using substrates such as stainless steel, polyethylene or polypropylene, which do not retain a residual, there is no reason to limit to the amount of peroxide which can be present in the vapor phase in the system during sterilization.

Detailed Description Text (14):
To further reduce water within the system, the chamber 2 may be dried prior to the introduction of hydrogen peroxide. Many means may be employed to drive water out of the chamber. Primarily, this is accomplished by vaporizing the water and pumping it out of the chamber. The vaporization can be accomplished with heat, plasma induction, vacuum or the like, either alone or in combination. Merely drawing a vacuum prior to introducing the hydrogen peroxide accomplishes a beneficial drying of the chamber 2. If the chamber 2 is heated during this process and if a high energy electromagnetic field is applied to urge the water into the plasma stage the drying is enhanced. U.S. Pat. No. 5,656,238 issued on Aug. 12, 1997 to Spencer at al. and incorporated herein by reference teaches such techniques in more detail.

Detailed Description Text (15):
Vaporization of the hydrogen peroxide can be achieved using well known methods as described above; FIGS. 6 to 8 show several new preferred methods. In FIG. 6, a chamber 30 is evacuated by a pump 32 separated from the chamber 30 by a throttle valve 34. A vaporizer 36 comprises a housing 38 in fluid communication with the chamber 30 and into which extends a liquid feeding nozzle 40 from outside of the chamber 30. A cup 42 within the housing 38 receives hydrogen peroxide from the nozzle 40. The hydrogen

peroxide can be vaporized as it exits the nozzle 40, or more preferably in a controlled fashion from the cup 42 by controlling the temperature of the cup 42 and the pressure in the chamber 30. Temperature control of the cup 42 can be as simple as thermally isolating it from the chamber 30, or a more active control system can be employed such a cooling coil or the like to maintain the cup 42 at a desired low temperature. Preferably, the entire vaporizer 36 is thermally isolated from the chamber 30 or temperature controlled in some fashion. Lower temperatures of vaporization enhance the preferential vaporization of water by exploiting the larger difference between the vapor pressures of water and hydrogen peroxide at lower temperatures. Creating a diffusion restriction 44 between the vaporizer 36 and chamber 30 enhances the preferential extraction of water vapor from the chamber as water vapor will more easily traverse the diffusion restriction and be pumped out of the chamber during the vaporization process. The diffusion restriction 44 may be simply reducing the clearance between the cup 42 and housing 38 through with the vapor must travel to reach the chamber 30.

Detailed Description Text (16):
FIG. 7 shows a similar chamber 50, pump 52 and valve 54 with modified vaporizer 56. The vaporizer 56 comprises a chamber 58 separated from the chamber 50 by a diffusion restriction 60, such as a permeable membrane. Liquid hydrogen peroxide solution enters the chamber 58 through a valve 62. FIG. 8 illustrates a similar arrangement with a chamber 70, pump 72, valve 74 and vaporizer 76 with a chamber 78 and valved hydrogen peroxide solution inlet 80. Restriction of the diffusion between the vaporizer chamber 78 and main chamber 70 is variable. During initial vaporization when primarily water is vaporizing the vapors pass through a tight diffusion restriction 82. After the concentration of the hydrogen peroxide solution reaches a given level valve 84 may be opened to speed the vaporization and diffusion of the concentrated hydrogen peroxide solution.

Detailed Description Text (18):
Tables 1 and 2 illustrate the effectiveness of the present invention. The experiments were run on a chamber of 73 liters at 45.degree. C. with 1480 mg of 59% hydrogen peroxide solution by weight. The vaporizer is separated from the chamber by twelve 2 mm diameter holes to effect diffusion restriction. Test A was conducted by opening the valve, evacuating the chamber to 0.3 torr. closing the valve, injecting the peroxide solution into the vaporizer, allowing the water and peroxide to vaporize and diffuse, and venting the chamber. Test B was conducted by injecting peroxide solution into the vaporizer at the atmospheric pressure, opening the valve, evacuating the chamber to 2 torr, closing the valve, allowing the remaining water and peroxide to vaporize and diffuse, and venting the chamber. Test C was conducted by opening the valve, evacuating the chamber, injecting the peroxide solution into the vaporizer when the chamber was evacuated to 30 torr, continuing to evacuate the chamber to 2 torr, closing the valve, allowing the remaining water and peroxide to vaporize and diffuse, and venting the chamber. The procedure for test D was same as test C except the peroxide solution was introduced into the vaporizer at 0.3 torr. Test E was conducted by opening the valve, evacuating the chamber to 0.3 torr, closing the valve, injecting the peroxide solution into the vaporizer, allowing the water and peroxide to vaporize and diffuse for 30 seconds, opening the valve, evacuating the chamber to 2 torr, closing the valve, allowing the remaining water oxide to vaporize and diffuse, and venting the chamber.

Detailed Description Text (20):
Monitoring of the temperature, pressure and hydrogen peroxide conditions within the chamber 30 (FIG. 6) allows the process to be controlled more precisely. Preferably, an automated control system, preferably employing a computer processor, receives signals of the temperature, pressure and perhaps also the hydrogen peroxide concentration and calculates the optimal pressure at which to maintain the chamber to remove the water from the hydrogen peroxide solution and from the chamber 30. It can also determine when the solution is sufficiently concentrated. For instance, it may be desired to only concentrate the solution to a certain degree so as to minimize the loss of hydrogen peroxide from the chamber, thereby minimizing hydrogen peroxide emissions from the chamber. While preferentially vaporizing the water from the solution, some hydrogen peroxide will also vaporize. Accordingly, one may wish to balance the efficient use of the quantity of hydrogen peroxide within the solution against the goal of eliminating all water from the solution and the chamber. By monitoring the ratio of water to peroxide in the vapor phase, the valve 34 can be controlled to remove the vapor until the desired ratio is achieved. The ratio can be determined using a hydrogen peroxide monitor and a moisture monitor, or by using a hydrogen peroxide monitor and a pressure sensor and then calculating the water using the PV=nRT equation and making the assumption that water and peroxide are essentially the only gases within the chamber

30.

Detailed Description Text (21):
It is known that certain spectra of light passing through the chamber can be measured to determine the hydrogen peroxide concentration. One particular method is disclosed in co-pending U.S. application Ser. No. 08/970,925 filed Nov. 14, 1997, incorporated herein by reference.

Detailed Description Text (22):
Table 3 compares a sterilization process in which the concentration of hydrogen peroxide is not increased with a process in which it is increased according to the present invention. The concentrations of water and peroxide for the normal process without concentrating the peroxide were calculated based on 1480 mg of 59% peroxide solution by weight in a 73 liters chamber. Test E procedure described in Table 1 was used to determine the concentrations of water and peroxide in the chamber with the concentrating process. The concentration of peroxide was measured with a peroxide monitor and the concentration of water was calculated from the pressure and peroxide monitor readings. Unlike the normal process which retains all the peroxide in the chamber, the concentrating process has less available peroxide in the chamber, but it removes more water than peroxide from the chamber and results in more concentrated peroxide for achieving better efficacy.

Detailed Description Text (23):
Table 4 also illustrates effects of the ratio of hydrogen peroxide vapor to water vapor in the chamber 30 on the ability to sterilize long narrow lumens or other diffusion restricted environments with Bacillus subtilis var. niger spores on stainless steel blades in 3 mm.times.500 mm stainless steel lumen. Water vapor was first introduced into the system and then essentially pure hydrogen peroxide vapor was introduced by liberation from a solid form. The lower concentrations of water show no failures, whereas with the higher ratio in the last column the efficacy decreased and in one test 3 out of 3 samples failed. Therefore, it is desirable to control the amount of water and peroxide in the chamber to achieve better efficacy.

Detailed Description Text (24):
Water vaporizes and diffuses faster than the peroxide under the same temperature and pressure conditions. At the beginning of the injection stage, the ratio of peroxide to water vaporized into the vapor phase is much lower than the ratio of peroxide to water in the liquid introduced into the vaporizer. By leaving the valve at the open position during the injection stage, more water can be removed from the chamber than the peroxide. As more water vaporized from the vaporizer and removed from the chamber, the peroxide concentration left in the system is increased. Table 5 shows the degree of concentration achieved according to the present invention by changing the pressure that the valve was closed during the concentrating process with the test E procedure described in Table 1. A total of 1480 mg 59% by weight hydrogen peroxide solution was used for each test. The results indicate that water is removed faster than the peroxide from the system and the wt% peroxide is increased by evacuating the system to a lower pressure.

Detailed Description Text (28):
The pressure and peroxide concentration curves during the concentrating process with 12% peroxide solution by weight are presented in FIG. 9. The chamber was set at 45.degree. C. The vaporizer has its own heater and is in communication with the chamber and separated from the chamber with the O-rings. Initially, the heater on the vaporizer was off and the vaporizer was heated to about 45.degree. C. due to the heated chamber and air around the vaporizer. As indicated from the pressure and peroxide concentration curves, the majority of molecules vaporized and diffused into the chamber during the first 15 minutes were water. Not much peroxide was vaporized and diffused into the chamber. This is consistent with the data published by Schumb et at., as shown in Table 9, that the concentration of hydrogen peroxide in the vapor phase over a 12% peroxide solution by weight, or 6.7% by mole, is less than 0.5% by mole under our test conditions.

Detailed Description Text (29):
As water and peroxide vaporized from the vaporizer, the vaporizer temperature decreased for more than 10.degree. C. With the valve at the open position while water and peroxide vaporized and diffused into the chamber, more water is removed from the system than the peroxide, and the peroxide concentration left in the vaporizer is increased. As indicated from the graph, the hydrogen peroxide concentration started to increase after 15 minutes. This indicated that the peroxide solution left in the vaporizer had

been concentrated by removing enough water from the vaporizer. The valve was then closed to retain the remaining peroxide vaporized into the sterilizer. The temperature of the vaporizer can then be optionally increased to enhance the vaporization of the remaining peroxide solution left in the vaporizer.

Detailed Description Text (31):
Tables 10A, 10B, and 10C have more detailed information about the peroxide to water ratio in the vapor phase at various temperatures and concentrations by re-calculating the mole fraction data in the Table 9. Since hydrogen peroxide, H.sub.2 O.sub.2, has one more oxygen than water, H.sub.2 O, the ratio of hydrogen peroxide to water based weight is larger than the ratio of hydrogen peroxide to water based on the mole.

Detailed Description Text (32):
Table 10A has the ratios of hydrogen peroxide to water in the vapor phase with 10%, 20% and 30% hydrogen peroxide solutions by mole under various temperatures.

Detailed Description Text (33):
Table 10B has the hydrogen peroxide to water ratios in the vapor phase with 40%, 50% and 60% hydrogen peroxide solutions by mole.

Detailed Description Text (34):
Table 10C has the hydrogen peroxide to water ratios in the vapor phase with 70%, 80% and 90% hydrogen peroxide solutions by mole.

Detailed Description Text (35):
By monitoring the concentration (i.e. the peroxide concentration or the ratio of hydrogen peroxide to water) during the sterilization cycle and controlling the timing to close the valve, it should be possible to achieve the long sought goal of parametric release. One could be assured that if the proper concentration was maintained for a sufficient period of time that a particular load of instruments placed within the chamber 30 and sterilized according to the present invention then the process would be sufficiently predictable so as to allow the load to be released for use without further checking with a biological indicator. Typically, such processes employ a biological indicator in the load, such as with a test load of microorganisms, which is then checked to ensure that sufficient sterilization has been achieved to kill all of the test microorganisms. With parametric release the time consuming process of biological indicators can be skipped.

Detailed Description Text (36):
As described preciously, shipping hydrogen peroxide solution with more than 60% by weight is regulated and can be difficult and impractical. One of the goals for this concentrating process is to concentrate the hydrogen peroxide solution in the system from less than 60% by weight to greater than 60% by weight. Therefore, more concentrated hydrogen peroxide can be generated during the process for a more efficacious cycle.

Detailed Description Text (37):
The process may be further enhanced by admitting sufficient hydrogen peroxide into the system so as to force some of the vaporized solution to condense upon the instruments being sterilized within the system. As described above, the solution can be vaporized by admitting it into the system at any pressure above the vapor pressures of water and hydrogen peroxide in the solution and then vaporized by reducing the pressure, or by admitting the solution at a pressure substantially below its vapor pressure whereupon it will start to vaporize thus releasing gas and increasing the pressure. In the second scenario if the pressure is then further reduced by pumping dorm the system, the concentration of the hydrogen peroxide in the system can be increased. This is especially true if the pressure rises to a level at least above the vapor pressure of hydrogen peroxide thereby limiting further vaporization of hydrogen peroxide from solution and encouraging some of the hydrogen peroxide to condense upon objects such as instruments within the system. Some of the water vapor would likely also condense in such event. By controlling the pressure, excess water vapor would be exhausted from the system and then the condensed solution would re-vaporize. To the extent that such solution had condensed within diffusion restricted areas the re-vaporization therein would further increase the concentration in those areas to enhance the sterilization efficacy therein. The quantity of solution admitted will primarily determine the pressure rise to initiate such condensation. The process is described in more detail in our co-pending U.S. application Ser. No. 09/223,594 filed Dec. 30, 1999 and entitled "Sterilization of Diffusion-Restricted Area by Re-Vaporizing the Condensed Vapor", which is incorporated herein by reference.

Detailed Description Text (38):
A typical cycle might comprise placing a load of instruments (not shown) within a CSR wrapped tray within the chamber 30 and then drawing a vacuum on the chamber 30 with the pump 32 down to below 1 torr or about 0.3 torr. An electromagnetic field applied to the chamber 30 at such time tends to drive any remaining water into the vapor or plasma stage so that the pump 32 can remove it. The pump 32 can be cycled or merely run continuously with the valve 34 controlling the vacuum process. Fresh dry air may be admitted to the chamber 30 raising the pressure back to atmosphere. Preferably the hydrogen peroxide solution, preferably a 59% hydrogen peroxide solution by weight, is admitted to the vaporizer 36 at atmospheric pressure and then the pump 32 exhausts the chamber 30 to a level at which the solution begins to vaporize. A monitor 100 for hydrogen peroxide vapor and monitor 102 (see FIG. 6) for water vapor in connection with an automated control system 104 can be employed to optimize the pressure conditions to enhance the initial vaporization and exhaust of water vapor. After the solution is sufficiently concentrated the temperature of the vaporizer 36 can be increased to vaporize the remaining solution. The valve 32 is closed to isolate the chamber 30 and the vaporized hydrogen peroxide solution is allowed to diffuse throughout the chamber to contact the instruments. Additional dry air or other gas can be admitted at this time to help push the sterilizing vapors into diffusion restricted areas, with the chamber 30 then further exhausted to resume a vacuum in the range of 2 to 10 torr. Additional admissions of air and vacuum can be employed especially in connection with additional admission and concentration of hydrogen peroxide solutions. After the hydrogen peroxide vapors have diffused throughout the chamber for a sufficient time an electromagnetic field may be applied to drive the vapor into the plasma stage and effect further sterilization. When the field is removed the activated species formed from the hydrogen peroxide recombine as water and oxygen, leaving little residual hydrogen peroxide. The chamber can be raised to atmospheric pressure and the load removed. If the ratio of hydrogen peroxide to water stays within the predetermined parameters the load can be released for use without further biological testing.

Detailed Description Paragraph Table (9):
TABLE 9 Vapor composition (mole fraction H2O2) over hydrogen peroxide water solutions Temp. Mole Fraction Hydrogen Peroxide in Liquid (.degree. C.) 10% 20% 30% 40% 50% 60% 70% 80% 90% 0 0.2% 0.6% 1.5% 3.1% 6.0% 11.2% 20.2% 35.2% 60.0% 10 0.3% 0.8% 1.8% 3.7% 7.0% 12.8% 22.4% 38.1% 62.6% 20 0.3% 0.9% 2.0% 4.1% 7.7% 13.8% 23.8% 39.7% 64.0% 25 0.3% 1.0% 2.2% 4.4% 8.1% 14.4% 24.7% 40.7% 64.8% 30 0.3% 1.0% 2.3% 4.6% 8.5% 15.1% 25.5% 41.7% 65.6% 40 0.4% 1.2% 2.6% 5.2% 9.4% 16.3% 27.2% 43.5% 67.1% 50 0.5% 1.4% 3.0% 5.7% 10.3% 17.5% 28.7% 45.2% 68.4% 60 0.5% 1.5% 3.3% 6.3% 11.1% 18.7% 30.2% 46.8% 69.6% 70 0.6% 1.7% 3.6% 6.8% 12.0% 19.9% 31.6% 48.2% 70.7% 80 0.7% 1.9% 4.0% 7.4% 12.8% 21.0% 32.9% 49.5% 71.6% 90 0.7% 2.1% 4.3% 8.0% 13.6% 22.1% 34.2% 50.8% 72.5% 100 0.8% 2.3% 4.7% 8.5% 14.4% 23.1% 35.4% 51.9% 73.3%

Detailed Description Paragraph Table (10):
TABLE 10A Ratio of peroxide to water in the vapor phase over hydrogen peroxide solutions 10% by mole or 20% by mole or 30% by mole or 17.3% by weight 32.1% by weight 44.7% by weight in solution in solution in solution Ratio of Ratio of Ratio of Ratio of Ratio of Ratio of peroxide to peroxide to peroxide to peroxide to peroxide to peroxide to water water water water water water Temp. in vapor in vapor in vapor in vapor in vapor in vapor (.degree. C.) by mole by weight by mole by weight by mole by weight 0 0.0020 0.0038 0.0060 0.0114 0.0152 0.0288 10 0.0030 0.0057 0.0081 0.0152 0.0183 0.0346 20 0.0030 0.0057 0.0091 0.0172 0.0204 0.0385 25 0.0030 0.0057 0.0101 0.0191 0.0225 0.0425 30 0.0030 0.0057 0.0101 0.0191 0.0235 0.0445 40 0.0040 0.0076 0.0121 0.0229 0.0267 0.0504 50 0.0050 0.0095 0.0142 0.0268 0.0309 0.0584 60 0.0050 0.0095 0.0152 0.0288 0.0341 0.0645 70 0.0060 0.0114 0.0173 0.0327 0.0373 0.0705 80 0.0070 0.0133 0.0194 0.0366 0.0417 0.0787 90 0.0070 0.0133 0.0215 0.0405 0.0449 0.0849 100 0.0081 0.0152 0.0235 0.0445 0.0493 0.0932

Detailed Description Paragraph Table (11):
TABLE 10B Ratio of peroxide to water in the vapor phase over hydrogen peroxide solutions 40% by mole or 50% by mole or 60% by mole or 55.7% by weight 65.4% by weight 73.9% by weight in solution in solution in solution Ratio of Ratio of Ratio of Ratio of Ratio of Ratio of peroxide to peroxide to peroxide to peroxide to peroxide to peroxide to water water water water water water Temp. in vapor in vapor in vapor in vapor in vapor in vapor (.degree. C.) by mole by weight by mole by weight by mole by weight 0 0.0320 0.0604 0.0638 0.1206 0.1261 0.2382 10 0.0384 0.0726 0.0753 0.1422 0.1468 0.2773 20 0.0428 0.0808 0.0834 0.1576 0.1601 0.3024 25 0.0460 0.0869 0.0881 0.1665 0.1682 0.3178 30 0.0482 0.0911 0.0929 0.1755 0.1779 0.3360 40 0.0549 0.1036 0.1038 0.1960 0.1947 0.3678 50 0.0604 0.1142 0.1148 0.2169 0.2121 0.4007 60 0.0672 0.1270 0.1249

0.2358 0.2300 0.4345 70 0.0730 0.1378 0.1364 0.2576 0.2484 0.4693 80 0.0799 0.1509
0.1468 0.2773 0.2658 0.5021 90 0.0870 0.1643 0.1574 0.2973 0.2837 0.5359 100 0.0929
0.1755 0.1682 0.3178 0.3004 0.5674

Detailed Description Paragraph Table (12):
TABLE 10C Ratio of peroxide to water in the vapor phase over hydrogen peroxide solutions 70% by mole or 80% by mole or 90% by mole or 81.5% by weight 88.3% by weight 94.4% by weight in solution in solution in solution Ratio of Ratio of Ratio of Ratio of Ratio of Ratio of peroxide to peroxide to peroxide to peroxide to peroxide to peroxide to water water water water water water Temp. in vapor in vapor in vapor in vapor in vapor in vapor (.degree. C.) by mole by weight by mole by weight by mole by weight 0 0.2531 0.4781 0.5432 1.0261 1.5000 2.8333 10 0.2887 0.5452 0.6155 1.1626 1.6738 3.1616 20 0.3123 0.5900 0.6584 1.2436 1.7778 3.3580 25 0.3280 0.6196 0.6863 1.2964 1.8409 3.4773 30 0.3423 0.6465 0.7153 1.3511 1.9070 3.6021 40 0.3736 0.7057 0.7699 1.4543 2.0395 3.8524 50 0.4025 0.7603 0.8248 1.5580 2.1646 4.0886 60 0.4327 0.8173 0.8797 1.6617 2.2895 4.3246 70 0.4620 0.8726 0.9305 1.7576 2.4130 4.5578 80 0.4903 0.9261 0.9802 1.8515 2.5211 4.7621 90 0.5198 0.9818 1.0325 1.9503 2.6364 4.9798 100 0.5480 1.0351 1.0790 2.0381 2.7453 5.1856

CLAIMS:

1. A method of sterilizing, and certifying as sterile, an article by furnishing concentrated hydrogen peroxide vapor to said article, the method comprising the steps of: a) placing the article into a sterilizer; b) introducing hydrogen peroxide and water into the sterilizer c) vaporizing said hydrogen peroxide and water to form a vapor comprising hydrogen peroxide and water; d) determining the concentration of hydrogen peroxide in the vapor; e) determining the concentration of water in the vapor; f) selectively drawing water vapor from the sterilizer to increase the ratio of hydrogen peroxide to water in the sterilizer; g) repeating steps c)-f) until the ratio of hydrogen peroxide to water is at a desired level; and h) furnishing the vaporized hydrogen peroxide to the article for a sufficient time to effect sterilization thereof and then certifying the sterility of said article based upon achieving said desired level.

2. A method according to claim 1 wherein the desired level is chosen from the group consisting of: i) attaining a ratio of hydrogen peroxide to water of at least 0.1 to 1 by weight, ii) attaining a ratio of hydrogen peroxide to water in the vapor which is at least two times higher than the ratio of hydrogen peroxide to water which is introduced into the sterilizer in step b), iii) attaining a concentration of hydrogen peroxide and water of at least 60% by weight of hydrogen peroxide, and iv) attaining a hydrogen peroxide concentration of at least 0.45 mg/L.

4. A method according to claim 1 wherein said sterilizer comprises a chamber and an enclosure, said enclosure is in fluid communication with the chamber and wherein the step of introducing hydrogen peroxide and water into the sterilizer comprises introducing the hydrogen peroxide and water into the enclosure.

6. A method according to claim 1 wherein the ratio of hydrogen peroxide to water introduced into the sterilizer is less than 0.1 to 1 by weight.

8. A method according to claim 7 wherein the sterilizer is evacuated to a pressure below the vapor pressure of the hydrogen peroxide and water in solution.

9. A method according to claim 1 wherein after the ratio of hydrogen peroxide to water is at said desired level a portion of the hydrogen peroxide is in liquid form and further comprising the step vaporizing said hydrogen peroxide which is in liquid form.

11. A method according to claim 1 and further comprising the step of monitoring the temperature of unvaporized hydrogen peroxide and water in the sterilizer.

12. A method according to claim 1 wherein the desired level comprises attaining a ratio of hydrogen peroxide to water of at least 0.1 to 1 by weight.

13. A method according to claim 1 wherein the desired level comprises attaining a ratio of hydrogen peroxide to water in the vapor which is at least two times higher than the ratio of hydrogen peroxide to water which is introduced into the sterilizer in step b).

14. A method according to claim 1 wherein the desired level comprises attaining a

concentration of hydrogen peroxide and water of at least 60% by weight of hydrogen peroxide.

15. A method according to claim 1 wherein the desired level comprises attaining a hydrogen peroxide concentration of at least 0.45 mg/L.

16. A method according to claim 1 wherein the ratio hydrogen peroxide to water introduced into the sterilizer comprises 12% or less hydrogen peroxide by weight.

19. A method according to claim 1 wherein the hydrogen peroxide vapor is furnished to the article for a period of at least 15 minutes.

20. A method according to claim 1 wherein the hydrogen peroxide vapor is furnished to the article for a period of at least 30 minutes.

L3: Entry 46 of 147 File: USPT Oct 1, 2002

DOCUMENT-IDENTIFIER: US 6458321 B1
TITLE: Sterilization system employing low frequency plasma

Abstract Text (1):
A method and system for sterilizing an article is provided that includes use of a low frequency (LF) gas discharge plasma. The method includes placing the article in a vacuum chamber and evacuating the vacuum chamber to a predetermined pressure. Gas or vapor species are introduced into the vacuum chamber, and a low frequency plasma is generated within the vacuum chamber, the low frequency plasma having a frequency of from 0 to approximately 200 kHz. The low frequency plasma is maintained for a time period sufficient to substantially remove gas or vapor species from the article. The sterilization system includes a vacuum chamber coupled to a vacuum pump and a vent, a first electrode, and a second electrode. The sterilization system further includes a first region within the vacuum chamber, the first region including a region between the first and second electrodes, and a second region within the vacuum chamber, the second region being in fluid communication with the first region. The sterilization system further includes a source of reactive agent species coupled to the vacuum chamber, a process control monitor, and a low frequency power module including components adapted to apply a low frequency voltage between the first electrode and second electrode to generate a low frequency plasma in the vacuum chamber, the low frequency voltage having a frequency of from 0 to approximately 200 kHz.

Brief Summary Text (5):
Plasmas produced using radio frequency (RF) generators in particular have proven to be valuable tools in processes for the sterilization of medical devices. For example, in U.S. Pat. Nos. 4,643,876 and 4,756,882, which are incorporated by reference herein, Jacobs, et al. disclose using hydrogen peroxide as a precursor in a low temperature sterilization system that employs RF plasma. The combination of hydrogen peroxide vapor and a RF plasma provides an efficient method of sterilizing medical devices without, using or leaving highly toxic materials or forming toxic by-products. Similarly, Jacob, U.S. Pat. No. 5,302,343, and Griffiths, et al., U.S. Pat. No. 5,512,244, teach the use of RF plasmas in a sterilization process.

Brief Summary Text (6):
However, there are problems associated with the use of an RF plasma in a sterilization process. The RF plasma may leave residual hydrogen peroxide on the sterilized article. The residual amount of hydrogen peroxide remaining on the sterilized article depends upon the RF power applied to the article, the amount of time exposed to the RF plasma, and the material of the article. For example, while some plastics (e.g., polyurethane) absorb hydrogen peroxide, other materials (e.g., Teflon) absorb relatively little, thereby yielding less residual hydrogen peroxide after sterilization.

Brief Summary Text (9):
One aspect of the present invention is a method of sterilization of an article. The method comprises placing the article in a vacuum chamber and evacuating the vacuum chamber to a predetermined pressure. Gas or vapor species are introduced into the vacuum chamber, and a low frequency plasma is generated within the vacuum chamber, the low frequency plasma having a frequency of from 0 to approximately 200 kHz. The low frequency plasma is maintained for a time period sufficient to substantially remove gas or vapor species from the article.

Brief Summary Text (10):
Another aspect of the present invention is a method of sterilization of an article. The method comprises placing the article in a vacuum chamber and evacuating the vacuum chamber to a predetermined pressure. A low frequency plasma is generated within the vacuum chamber, the low frequency plasma having a frequency of from 0 to approximately

200 kHz. The low frequency plasma is maintained for a time period sufficient to heat the article to aid the evaporation and removal of water and other absorbed gases from the vacuum chamber and the article.

Brief Summary Text (11):
Another aspect of the present invention is a system for sterilizing an article. This system comprises a vacuum chamber coupled to a vacuum pump and a vent, a first electrode, and a second electrode. The system further comprises a first region within the vacuum chamber, the first region comprising a region between the first and second electrodes. The system further comprises a second region within the vacuum chamber, the second region being in fluid communication with the first region. The system further comprises a source of fluid coupled to the vacuum chamber, a process control monitor, and a low frequency power module comprising components adapted to apply a low frequency voltage between the first electrode and second electrode to generate a low frequency plasma in the vacuum chamber, the low frequency voltage having a frequency of from 0 to approximately 200 kHz.

Detailed Description Text (5):
The vacuum chamber 12 of the preferred embodiment is sufficiently gas-tight to support a vacuum of approximately less than 40 Pa (0.3 Torr). Coupled to the vacuum chamber 12 is a pressure monitor (not shown) which is also coupled to the process control module to provide a measure of the total pressure within the vacuum chamber. Also coupled to the vacuum chamber 12 is the reactive agent monitor 34 which is capable of detecting the amount of the reactive agent in the vacuum chamber 12. In the exemplary embodiment of the present invention, the reactive agent is hydrogen peroxide, and the reactive agent monitor 34 measures the absorption of ultraviolet radiation at a wavelength characteristic of hydrogen peroxide. Other methods of reactive agent detection compatible with the present invention include, but are not limited to, pressure measurement, near infrared absorption, and dew point measurement. The reactive agent monitor 34 is also coupled to the process control module 30 to communicate the detected amount of the reactive agent to the process control module 30.

Detailed Description Text (6):
In the preferred embodiment of the present invention, inside and electrically isolated from the vacuum chamber 12 is the electrode 32, which is electrically conductive and perforated to enhance fluid communication between the gas and plasma species on each side of the electrode 32. The electrode 32 of the preferred embodiment generally conforms to the inner surface of the vacuum chamber 12, spaced approximately one to two inches from the wall of the vacuum chamber 12, thereby defining a gap region between the vacuum chamber 12 and the electrode 32. The electrode 32 is coupled to the LF power module 22 via the LF voltage conduit 24. In the preferred embodiment, with the vacuum chamber 12 connected to electrical ground via a bypass capacitor and shunt resistor, application of an LF voltage between the vacuum chamber 12 and the electrode 32 creates an LF electric field which is stronger in a first region 31 which includes the gap region and the vicinity of the edges of the electrode 32. The LF electric field is weaker in a second region 33 where the sterilized articles are placed. Generally, in other embodiments, the LF electric field can be generated by applying an LF voltage between the electrode 32 and a second electrode in the vacuum chamber 12. In such embodiments, the first region 31 includes the gap region between the two electrodes, and the vicinity of the edges of one or both of the electrodes. The preferred embodiment in which the vacuum chamber 12 serves as the second electrode is one of the many different ways to generate the gas plasma.

Detailed Description Text (7):
In the preferred embodiment illustrated in FIG. 2A, a cylindrically-shaped electrode 32 provides fluid communication between the gas and plasma on each side of the electrode 32 through the open ends of the electrode 32 as well as through the perforations in the side of the electrode 32. These open ends and perforations permit gaseous and plasma species to freely travel between the first region 31 between the electrode 32 and the walls of the vacuum chamber 12 and the second region 33 where the sterilized articles are placed. Similarly, as illustrated in FIGS. 2B-2I, other configurations of the electrode 32 provide fluid communication between the first region 31 and the second region 33. FIG. 2B schematically illustrates a cylindrically-shaped electrode 32 with open ends and, louvered openings along its sides. FIG. 2C schematically illustrates a cylindrically-shaped electrode 32 with open ends and solid sides. FIG. 2D schematically illustrates an electrode 32 comprising a series of colinear cylindrically-shaped segments with open ends and solid sides. FIG. 2E schematically illustrates an electrode 32 with a partial cylindrical shape, open ends and solid sides. FIG. 2F schematically illustrates a cylindrically-symmetric and longitudinally-asymmetric electrode 32 with

open ends and solid sides. FIG. 2G schematically illustrates an asymmetric electrode 32 with open ends and solid sides. More than one electrode can be used to generate the plasma. FIG. 2H schematically illustrates an electrode system with a first electrode 32 that is cylindrically-shaped with open ends and solid sides, and a second electrode 32' comprising a wire substantially colinear with the first electrode 32. The LF voltage is applied between the first electrode 32 and the second electrode 32'. In this embodiment, the first region 31 is the region between the first electrode 32 and the second electrode 32', and the second region 33 is between the first electrode 32 and the vacuum chamber 12. FIG. 2I schematically illustrates a generally square or rectangular electrode within a generally square or rectangular vacuum chamber. The various configurations for generally cylindrical electrodes schematically illustrated in FIGS. 2A-2H can also be applied to the generally square or rectangular electrode of FIG. 2I. Each of these embodiments of the electrode 32 provide fluid communication between the first region 31 and the second region 33.

Detailed Description Text (9):
The reactive agent source 18 of the preferred embodiment is a source of fluid coupled to the vacuum chamber 12 via the reactive agent line 19 and the reactive agent valve 20. The reactive agent valve 20 is coupled to, and controlled by, the process control module 30. The reactive agent source 18 of the preferred embodiment comprises reactive agent species. In the preferred embodiment, the reactive agent species comprises a germicide which is a sterilant or a disinfectant, such as hydrogen peroxide. In addition, the germicide supplied by the reactive agent source 18 can be in gas or vapor form. By opening the reactive agent valve 20, reactive agent atoms and molecules from the reactive agent, source 18 can be transported into the vacuum chamber 12 via the reactive agent line 19. In certain embodiments, the reactive agent valve 20 is capable of being opened to variable degrees to adjust the pressure of the reactive agent in the vacuum chamber 12. In the exemplary embodiment of the present invention, the reactive agent species of the reactive agent source 18 comprising hydrogen peroxide molecules.

Detailed Description Text (26):
The electronics for RF sterilizers are complicated by the need of such systems to attempt to closely match the output impedance of the RF generator with the plasma impedance at all times in order to maximize power efficiency and to avoid damage to the RF generator. Plasma impedance varies widely during plasma formation, being very high until the plasma is fully formed, and very low thereafter. When first igniting a plasma, the RF generator cannot match the high plasma impedance which exists prior to the full formation of the plasma, so a large fraction of the power output is reflected back to the RF generator. RF generators have protection systems which typically limit the RF generator output during periods of high reflected power to avoid damage. However, to ignite the plasma, the voltage output of the RF generator must exceed the threshold voltage required for plasma ignition. The threshold voltage is dependent on the chamber pressure, reactive agent, and other operating parameters and is approximately 300 V.sub.rms. In an RF system, once ignition has been achieved, and the plasma impedance is thereby reduced, the magnitude of the applied RF voltage must be reduced to a sustaining voltage, e.g., approximately 140 V.sub.rms, to avoid excessive power delivery. Because the higher RF voltages required for plasma ignition produce excessively high reflected power before full plasma formation, RF generators require complicated safeguards to prevent damage during the plasma ignition stage.

Detailed Description Text (27):
Conversely, the complexity and rate of ignition failures are significantly reduced for LF sterilizers since the LF sterilizers may operate using applied voltages above the threshold voltage and have much less restrictive output impedance matching requirements. During the times at which the applied LF voltage equals zero, as seen in FIG. 5A, the LF plasma is extinguished and there is no LF plasma in the vacuum chamber. The LF plasma must then be re-ignited twice each cycle. By only operating in one voltage regime, LF sterilizers have simpler and more reliable electrical systems than do RF sterilizers. These electrical systems are easier to service and diagnose, thereby reducing the costs associated with repair. In addition, the higher peak plasma densities resulting from LF sterilizers likely result in increased dissociative recombination on the articles, thereby reducing the amount of residual reactive species remaining on the articles after the sterilization procedure.

Detailed Description Text (30):
In the preferred process, upon reaching a desired chamber pressure, the vacuum valve 16 is closed, and the reactive agent valve 20 is opened under the control of the process control module 30, thereby injecting 230 reactive agent from the reactive agent source 18 into the vacuum chamber 12 via the reactive agent line 19. In the preferred

embodiment, the reactive agent comprises hydrogen peroxide, which is injected in the form of a liquid which is then vaporized. The injected liquid contains preferably from about 3% to 60% by weight of hydrogen peroxide, more preferably from about 20% to 60% by weight of hydrogen peroxide, and most preferably from about 40% to 60% by weight of hydrogen peroxide. The concentration of hydrogen peroxide vapor in the vacuum chamber 12 may range from 0.125 to 20 mg of hydrogen peroxide per liter of chamber volume. The higher concentrations of hydrogen peroxide will result in shorter sterilization times. Air or inert gas such as argon, helium, nitrogen, neon, or xenon may be added to the chamber with the hydrogen peroxide to maintain the pressure in the vacuum chamber 12 at the desired level. This injection 230 of reactive agent may occur as one or more separate injections.

Detailed Description Text (32):
The vacuum chamber 12 is then partially evacuated 250 by pumping out a fraction of the reactive agent from the vacuum chamber 12 by controllably opening the vacuum valve 16 under the control of the process control module 30. Once the vacuum pressure within the vacuum chamber 12 has reached the desired pressure, the vacuum valve 16 is controllably adjusted to maintain the desired pressure, and the process control module 30 signals the LF power module 22 to energize the electrode 32 within the vacuum chamber 12. In the preferred embodiment in which the reactive agent comprises hydrogen peroxide, the pressure of the hydrogen peroxide in the vacuum chamber 12 is preferably less than approximately 670 Pa (5 Torr), more preferably between approximately 25 and 270 Pa (0.2 to 2 Torr), and most preferably between approximately 40 and 200 Pa (0.3 to 1.5 Torr). By applying a LF voltage to the electrode 32, the LF power module 22 generates 260 a reactive agent LF plasma inside the vacuum chamber 12 by ionizing the reactive agent. The article is exposed to the reactive agent LF plasma for a controlled period of time. In the preferred embodiment, an additional cycle 275 is performed. Other embodiments may omit this additional cycle 275, or may include further cycles.

Detailed Description Text (33):
In both RF and LF plasmas, the components of the reactive agent plasma include dissociation species of the reactive agent and molecules of the reactive agent in excited electronic or vibrational states. For example, where the reactive agent comprises hydrogen peroxide as in the preferred embodiment, the reactive agent plasma likely includes charged particles such as electrons, ions, various free radicals (e.g., OH, O.sub.2 H), and neutral particles such as ground state H.sub.2 O.sub.2 molecules and excited H.sub.2 O.sub.2 molecules. Along with the ultraviolet radiation produced in the reactive agent plasma, these reactive agent species have the potential to kill spores and other microorganisms.

Detailed Description Text (39):
The fraction of the charged particles created in the reactive agent LF plasma which enter the second region 33 is a function of the frequency of the applied electric field. The charged particles have two components to their motion--random thermal speed and drift motion due to the applied electric field. The thermal speed, measured by the temperature, is the larger of the two (typically approximately 10.sup.7 -10.sup.8 cm/sec for electrons), but it does not cause the charged particles to flow in any particular direction. Conversely, the drift speed is directed along the electric field, resulting in bulk flow of charged particles in the direction of the applied electric field. The magnitude of the drift speed is approximately proportional to the magnitude of the applied electric field, and inversely proportional to the mass of the charged particle. In addition, the magnitude of the drift speed is dependent on the gas species and chamber pressure. For example, for typical operating parameters of gas discharge plasma sterilizers, including an average electric field magnitude of approximately 1 volt/cm, the drift speed for an electron formed in a gas discharge plasma is typically approximately 10.sup.6 cm/sec.

Detailed Description Text (47):
The LF plasma provides a reduction of the amount of residual reactive agent molecules remaining on the articles after the sterilization procedure is complete. Where the reactive agent comprises hydrogen peroxide, the amount of residual hydrogen peroxide remaining on the sterilized articles is preferably less than approximately 8000 ppm, more preferably less than approximately 5000 ppm, and most preferably less than approximately 3000 ppm. In a comparison of the amount of residual hydrogen peroxide remaining after a LF plasma sterilization as compared to a RF plasma sterilization, nine polyurethane test samples were exposed to hydrogen peroxide during a simulated sterilization cycle in both a LF sterilizer and a RF sterilizer. Each sample was prepared by washing with Manuklenz.RTM. and drying prior to sterilization to avoid any cross contamination. The nine samples were then distributed uniformly across the top

shelf of a standard industrial rack.

Detailed Description Text (48):
A full LF sterilization cycle, which matched nearly exactly the conditions of a standard RF sterilizer cycle, was used to perform the comparison. The full LF sterilization cycle included a 20-minute exposure to a pre-injection plasma, a first 6-minute hydrogen peroxide injection, a vent to atmosphere, a 2-minute diffusion, a first 2-minute post-injection plasma, a second 6-minute hydrogen peroxide injection, a vent to atmosphere, a 2-minute diffusion, a second 2-minute post-injection plasma, and a vent to atmosphere. Two fill LF sterilization cycles were performed and compared to two full RF sterilization cycles. As seen in Table 1, all parameters other than the post-injection plasma power were maintained as constant as possible from run to run.

Detailed Description Text (51):
Exposure to a LF post-injection plasma reduced the residual reactive species more effectively than did exposure to a RF post-injection plasma of comparable power. LF Run 1 had approximately 23% less residual hydrogen peroxide than either RF Run 1 or RF Run 2, even though all had approximately the same post-injection plasma power. The LF processes therefore resulted in less residual hydrogen peroxide than did the corresponding RF process.

Detailed Description Text (52):
The comparison of the two LF sterilization cycles illustrates that increased plasma power results in a reduction of the hydrogen peroxide residuals. Furthermore, the variation between samples, as indicated by the standard deviation of the residual measurements, was significantly reduced in the LF process, thereby indicating an increased uniformity as compared to the RF process.

CLAIMS:

1. A method of sterilization of an article, the method comprising: placing the article in a first region of a vacuum chamber; evacuating the vacuum chamber to a predetermined pressure; introducing gas or vapor species into the vacuum chamber; generating a plasma within the vacuum chamber by applying an applied electric field in a second region of the vacuum chamber, the second region in fluid communication with the first region, the first region having an electric field weaker than the applied electric field in the second region, the applied electric field having a frequency of less than 10 kHz; and maintaining the plasma for a time period sufficient to substantially remove gas or vapor species from the article.

2. The method as defined in claim 1, wherein the gas or vapor species comprises hydrogen peroxide.

3. The method as defined in claim 2, wherein the concentration of the hydrogen peroxide is at least 0.125 mg/liter.

4. The method as defined in claim 2, wherein an amount of hydrogen peroxide remaining on the article after maintaining the plasma is less than approximately 8000 ppm.

10. A method of sterilization of an article, the method comprising: placing the article in a first region of a vacuum chamber; evacuating the vacuum chamber to a predetermined pressure; generating a plasma within the vacuum chamber by applying an applied electric field in a second region of the vacuum chamber, the second region in fluid communication with the first region, the first region having an electric field weaker than the applied electric field in the second region, the applied electric field having a frequency of less than 10 kHz; and maintaining the plasma for a time period sufficient to heat the article to aid the evaporation and removal of water and other absorbed gases from the vacuum chamber and the article.

16. A system for sterilizing an article, the system comprising: a first electrode; a vacuum chamber coupled to a vacuum pump and a vent, wherein the vacuum chamber comprises a second electrode; a first region within the vacuum chamber, the first region comprising a region between the first and second electrodes; a second region within the vacuum chamber, the second region being in fluid communication with the first region, the second region adapted to receive the article; a source of fluid coupled to the vacuum chamber; a process control module; and a power module comprising components adapted to apply a voltage between the first electrode and second electrode so as to generate a plasma in the first region within the vacuum chamber, the voltage having a frequency of less than 10 kHz.

19. The system as described in claim 18, wherein the germicide comprises hydrogen peroxide.

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L3: Entry 53 of 147 File: USPT Apr 2, 2002

DOCUMENT-IDENTIFIER: US 6365102 B1
**** See image for Certificate of Correction ****
TITLE: Method of enhanced sterilization with improved material compatibility

Abstract Text (1):
A method of enhanced sterilization with improved material compatibility. The following enhancements have been made. First, repeated venting, evacuation, and plasma treatments can be performed in the pre-plasma stage. Second, a lower power level can be used in the post-plasma stage than in the pre-plasma stage. Third, after the post-plasma stage, the chamber can be held at atmospheric pressure or sub-atmospheric pressure for a period of time after venting, before re-evacuating the chamber, rather than evacuating after the chamber is vented to atmospheric pressure or sub-atmospheric pressure. Any of the three enhancements may be used separately, and it is not necessary to practice all three enhancements to obtain at least some of the benefits of enhanced sterilization with improved material compatibility.

Brief Summary Text (6):
The STERRAD Sterilization Process is performed in the following manner. The items to be sterilized are placed in the sterilization chamber, the chamber is closed, and a vacuum is drawn. An aqueous solution of hydrogen peroxide is injected and vaporized into the chamber so that it surrounds the items to be sterilized. After reduction of the pressure in the sterilization chamber, a low-temperature gas plasma is initiated by applying radio frequency energy to create an electrical field. In the plasma, the hydrogen peroxide vapor is dissociated into reactive species that collide/react with and kill microorganisms. After the activated components react with the organisms or with each other, they lose their high energy and recombine to form oxygen, water, and other nontoxic byproducts. The plasma is maintained for a sufficient time to achieve sterilization and remove residuals. At the completion of the process, the RF energy is turned off, the vacuum is released, and the chamber is returned to atmospheric pressure by the introduction of High Efficiency Particulate-Filtered Air (HEPA).

Brief Summary Text (9):
For optimum operation, a plasma sterilization system such as that described above requires the loads that are to be sterilized to be quite dry. However, normal hospital practice in the preparation of instruments for sterilization often results in levels of water that may be excessive. The excess water makes it difficult to achieve the low-pressure thresholds required to initiate the sterilization process. To initiate the sterilization process, the chamber pressure is preferably reduced to relatively low levels, for example approximately 200-700 mTorr. Since the equilibrium vapor pressure of water is significantly higher than 700 mTorr at room temperature, any water in the chamber or load will begin to vaporize during the vacuum phase. The heat of vaporization required for the water to vaporize causes the load and any remaining water to chill. When enough water has vaporized, the remaining liquid begins to freeze. Eventually, the remaining liquid will completely freeze, which slows the rate of vapor generation and retards the attainment of the pressure levels required for optimum operation of the sterilizer. These conditions can cause undesirably long sterilization cycles or even cancellation of the sterilization cycle. Spencer et al. (U.S. Pat. No. 5,656,238) disclosed that plasma can be used to enhance the drying so that the desired pressure for sterilization may be achieved more quickly.

Brief Summary Text (12):
One aspect of the invention involves a method of sterilizing articles in a load in a chamber with a chemical sterilant. The method includes conditioning the load, then introducing chemical sterilant; and maintaining to achieve sterilization. Conditioning the load includes evacuating the chamber, generating plasma in the chamber, venting the chamber to approximately atmospheric or subatmospheric pressure, and repeating the

evacuating, generating plasma, and venting at least two times.

Brief Summary Text (13):
Preferably, conditioning the load includes increasing the temperature of at least a portion of the load to at least 30.degree. C. Advantageously, conditioning the load comprises increasing the temperature of at least a portion of the load to at least 35.degree. C. In a preferred embodiment, the chemical sterilant is hydrogen peroxide.

Brief Summary Text (19):
Preferably, the chemical sterilant is hydrogen peroxide. Advantageously, the method also includes venting the chamber and evacuating the chamber after generating plasma with the higher power level.

Brief Summary Text (21):
Another aspect of the invention involves a method of sterilizing articles in a load with a chemical sterilant in a chamber with improved material compatibility. The method involves evacuating the chamber, generating plasma with a first power level, venting the chamber to a pressure, evacuating the chamber, and introducing chemical sterilant into the chamber. Introducing the sterilant occurs after generating plasma with the first power level. The chamber is evacuated, plasma with a second power level is generated, where the plasma with the second power level is generated after the sterilant is introduced. The method also includes venting the chamber, where the venting occurs after generating plasma with the second power level. The chamber is then evacuated and vented. The first power level is higher than the second power level, thereby sterilizing the articles with improved material compatibility. Advantageously, the chemical sterilant is an antimicrobial agent. Preferably, the antimicrobial agent is hydrogen peroxide.

Detailed Description Text (2):
Referring to the drawings, FIG. 1 depicts a sterilizer in block diagram form generally at 10. The sterilizer 10 and its components and methods of use are described more fully in U.S. Pat. 4,756,882, issued Jul. 12, 1988. This patent is incorporated by reference herein. Other sterilizers are suitable for the method of the invention, and the sterilizer of FIG. 1 is not meant to be limiting to the method. The sterilizer 10 includes a vacuum chamber 12, a vacuum pump 14 connected to the vacuum chamber 12 by a valve 16, and a source of suitable reactive agent 18 such as hydrogen peroxide connected to the vacuum chamber 12 by a line having a valve 20 therein. The sterilizer 10 also includes an RF generator 22 electrically connected to the plasma generator inside the vacuum chamber 12 by a suitable coupling 24, as well as a HEPA vent 26 connected to the vacuum chamber via a line and a valve 28. A process control logic 30, preferably a programmable computer, is connected to each of the components which are connected to the vacuum chamber 12. The process control logic 30 directs the operation of each of the components connected to the vacuum chamber at the appropriate time to effectuate the sterilization operation.

Detailed Description Text (3):
The vacuum chamber 12 contains the objects to be sterilized and is sufficiently gas-tight to support a vacuum of less than 300 mTorr. Inside the chamber 12 is an RF antenna, or electrode array 32 to which the RF energy is supplied. In one preferred embodiment the electrode is arranged such that it is tubular and equidistant from the chamber 12 wall to produce a symmetric RF electric field distribution. In another embodiment, the electrode and chamber are in a rectangular shape so as to provide more usable space. The electrode excites a plasma when an RF potential is applied by the RF generator 22 through the RF coupling 24. The RF coupling 24 may be a coaxial cable or other such waveguide capable of transmitting high power RF energy without significant impedance loss connected to an impedance matching device for the electrode.

Detailed Description Text (8):
When the desired pressure has been reached, the process control logic 30 transmits a signal to the RF generator 22 to energize the electrode 32 within the chamber 12. This action causes a gas plasma to be created inside the chamber comprised of residual gas species, step 40 of FIG. 2. Because the articles to be sterilized are loaded into the chamber in the presence of air and moisture, the residual gases at this stage are mainly air and moisture.

Detailed Description Text (9):
As described in U.S. Pat. No. 5,656,238, hereby incorporated by reference, energy is transferred to condensed water in the chamber, thereby aiding the drying of the chamber and the equipment in the chamber. While plasma is being generated, the vacuum pump 14

remains engaged to further evacuate the chamber and remove residual gases and moisture from the chamber. This step is labeled as plasma enhanced conditioning, step 42, in FIG. 2, and the pressure in the chamber is curve 44 of FIG. 4. After a period of time, approximately 1-60 minutes, more preferably 2-40 minutes and most preferably 5-20 minutes, the plasma generator is turned off or quenched, step 46 in FIG. 2. The plasma processing conditioning of step 42 has also been described as "pre-plasma", because the plasma process takes place before injection of the reactive agent 18 or sterilant. At this point in the process, the evacuation can be continued, or, alternatively, the chamber can be vented, step 48 of FIG. 2 and curve 50 of FIG. 4. It is generally preferred to vent the chamber, because the venting helps in the drying process. The chamber can be vented to atmospheric or subatmospheric pressure. In some embodiments, the chamber can be vented to a pressure higher than atmospheric pressure, though this is not preferred. The steps in FIG. 2 are optional steps to condition the load. If the load does not require conditioning, the cycle can be started from the sterilization steps shown in FIG. 3.

Detailed Description Text (10):
The sterilization cycle starts from step 52 of FIG. 3 and curve 54 of FIG. 4. The chamber is evacuated to a pressure less than or equal to 10,000 mTorr, more preferably 100-5000 mTorr, and most preferably 300-1000 mTorr. When the desired vacuum threshold has been reached, the reactive agent 18 or sterilization agent is injected in step 56 of FIG. 3. The injection of the sterilization agent during step 56 causes the pressure inside the chamber to rapidly rise. In the preferred embodiment, the pressure may rise to a level of approximately 3000 mTorr or more, as indicated by the curve 58 in FIG. 4. The sterilization agent is preferably aqueous hydrogen peroxide, though other sterilization agents such as anhydrous peroxide generated from solid peroxide complexes, chlorine dioxide, ozone, ethylene oxide, peracetic acid, and other agents can also be used. The injection phase takes approximately 1-60 minutes.

Detailed Description Text (15):
After the sterilization process is complete, the current is shut off to the plasma generator, quenching the plasma, step 72 of FIG. 3. The chamber 12 is then vented to approximately atmospheric pressure through the HEPA vent 26 during the vent step 74 of FIG. 3. The pressure in the chamber during the venting step is shown by curve 76 of FIG. 4. The vent after the post-plasma stage helps to carry heat from the electrode and chamber walls to the instruments in the load. Very little heat is transferred from the electrode and chamber walls to the load during the post-plasma stage, curve 68 of FIG. 4, because the vacuum in the chamber does not effectively transfer heat. Venting the chamber allows for heat transfer from the electrode and chamber walls to the load.

Detailed Description Text (20):
As a brief introduction to the various embodiments of the enhanced sterilization method, the first enhancement is to alternately evacuate, treat with pre-plasma, and vent the chamber multiple times during the pre-plasma stage, as shown in FIG. 6. The pulsing of pre-plasma with venting has been found to improve the sterilization efficiency of the process. Although we do not wish to be tied to a theory as to why the pulsing improves the sterilization efficiency, it is believed that when the plasma is generated, the electrode and surrounding walls become hotter than the load, which is usually at ambient temperature when initially placed in the chamber. The multiple vents carry heat from the electrode and walls to the load to be sterilized. It is likely that the higher load temperature allows better evaporation of the chemical sterilant at subambient pressure when it is injected into the chamber later in the process, enhancing penetration to areas of close contact on the devices to be sterilized and achieving better sterilization lethality or sterilization efficiency. The venting pressure during the pre-plasma pulsing can be any pressure higher than the plasma-enhanced conditioning pressure. Also, the venting stage can have a holding period to enhance the heat transfer to the load. The effectiveness of the pulsing during the pre-plasma stage for enhancing the sterilization efficiency will be demonstrated in the Examples below. It is to be understood that other means of heat source can be employed to enhance heat transfer, such as a conventional heater or infrared lamp, with or without circulating means.

Detailed Description Text (21):
The second enhancement is to maintain the vent after the post-plasma stage for an extended period of time before evacuating, rather than evacuating immediately after reaching atmospheric pressure, as in curves 76 and 80 of FIG. 4. Maintaining the chamber at atmospheric pressure or subatmospheric pressure for an extended period of time has been found to reduce the residual level of sterilant on the sterilized devices.

Detailed Description Text (24):
Without wishing to be tied to a theory for the reason for the improved material compatibility by using different RF levels, it seems likely that the improvement in material compatibility is due to the different reactivities of the plasmas formed in the pre-plasma stage and the post-plasma stage. The plasma in the pre-plasma stage is formed from air and moisture, and the plasma in the post-plasma stage is formed from a mixture of air and sterilization agent, normally hydrogen peroxide. The plasma formed from the mixture of air and sterilization agent is more reactive than the plasma formed from air and moisture. It is believed that a higher RF power level can be used in the pre-plasma stage than in the post-plasma stage without affecting material compatibility, because the pre-plasma plasma is less reactive.

Detailed Description Text (29):
After the final vent in the pre-plasma stage of the enhanced method, the chamber is evacuated to less than or equal to 10,000 mTorr, more preferably to 100-5000 mTorr, and most preferably to 300-1000 mTorr, step 52 of FIG. 3, the reactive agent is injected, step 56, the reactive agent is allowed to diffuse with or without a vent, step 60, and the chamber is evacuated, step 62. The pressure curves for these steps are shown as curves 54, 58, 61, and 64 in FIG. 6. This portion of the enhanced method is identical to the method shown in FIG. 4. It seems likely that the increased temperature of the load due to the pulsing in the pre-plasma stage increases the volatility of the sterilant, enhances the overall available sterilant concentration in the vapor phase, and improves the penetration and sterilization effectiveness of the sterilant vapor.

Detailed Description Text (32):
While we do not wish to be tied to a theory as to the reason for the improved material compatibility by using different power levels while generating the two forms of plasma , the plasma in the pre-plasma treatment is generated from air and moisture, while the plasma in the post-plasma treatment is generated with a mixture of air, moisture, and the reactive agent 18. The reactive agent is typically hydrogen peroxide and, or, other sterilants, and the plasma generated from chemical sterilant is more reactive than the plasma generated from air and moisture. It seems likely that use of a lower power level in the post-plasma stage than in the pre-plasma stage reduces damage to the materials inside the sterilization chamber due to the reactive plasma formed from the air/hydrogen peroxide in the chamber in the post-plasma stage. The lower power level in the post-plasma stage leads to improved material compatibility.

Detailed Description Text (33):
After the plasma in the post-plasma stage is quenched (step 72 of FIG. 3), the chamber 12 is vented, step 74 of FIG. 3 and curve 76 of FIG. 6. In the enhanced method of the present invention, the chamber 12 is held at approximately atmospheric pressure or subatmospheric pressure after the vent, an additional step 86, not shown on FIG. 3. The additional step takes place between the vent step 74 and the evacuate step 78 of FIG. 3. The pressure curve of the hold step is shown as 86 on FIG. 6. The vent, hold, evacuate curves are shown as curves 76, 86, and 80 of FIG. 6 and can be compared to curves 76 and 80 of FIG. 4, without the hold step. During the hold step, the pressure in the chamber is held at approximately atmospheric pressure or sub-atmospheric pressure for a period of 0.1 to 300 minutes, more preferably 1 to 60 minutes, and most preferably 1 to 20 minutes. Without wishing to be tied to a theory for the reason for the benefit, it seems likely that during the hold step, heat from the hotter electrode and the hotter walls can be transferred to the load, heating the load. It is believed that the higher temperature load increases the volatility of the residual sterilant on the instruments, leading to lower residual levels on the instruments when the chamber is evacuated after the hold step. Heating at least a portion of the load to a temperature above ambient temperature, more preferably to a temperature above 30.degree. C., and most preferably to a temperature above 35.degree. C. has been found to be effective in reducing the residual level of sterilant on the load. The reduced residuals on the sterilized equipment with the hold step and the preferred length of time for the hold step are shown in the Examples below.

Detailed Description Text (45):
In the following example, stainless steel coupons inoculated with >10.sup.6 Bacillus stearothermophilus spores were placed inside a 1 mm ID.times.2000 mm long polyethylene (PE) lumen, attached with a vessel containing liquid sterilant, 142 .mu.L of 48% by weight aqueous hydrogen peroxide (U.S. Pat. No. 4,913,414). Placement of the inoculated coupon in the lumen was accomplished with a coupon holder (3 mm ID.times.15 mm long) located at approximately 1500 mm from the vessel containing the liquid sterilant. Lumens with the inoculated coupons were placed in each of the trays containing sets of

various medical devices. The trays were wrapped with sterilization wrap, sealed with sterilization tape, placed within a 270 liter sterilization chamber and treated with various forms of the enhanced sterilization cycle shown in FIG. 6.

Detailed Description Text (46):
The sterilization chamber with the lumens and inoculated coupons was evacuated to 600 mTorr, plasma was generated for a total of 20 or 35 minutes with the RF setting shown in the Table below, the plasma was quenched, the chamber was vented to one atmosphere, and the chamber was evacuated to a pressure of 600 mTorr. At this point, in some experiments, one or more additional vent/evacuate/plasma cycles were performed, as shown in pressure curves 50, 38, and 44 of FIG. 6. The length of time in minutes for the pre-plasma treatments is shown as a numerical figure in bold in the second column of Table 1 below. The experiments with multiple bold figures are experiments in which multiple plasma/vent cycles were performed. If only one pre-plasma treatment was done, there is only a single bold number in the Table. The figure in bold indicates the number of minutes that plasma was generated for each cycle.

Detailed Description Text (47):
After the last pre-plasma treatment, the chamber was vented to one atmosphere, evacuated to 600 mTorr, 9.3 mg/L of 59% hydrogen peroxide was injected, increasing the pressure in the chamber to approximately 8000 mTorr. After the 6.5 minute injection step, the chamber was vented to one atmosphere pressure to allow the hydrogen peroxide to diffuse for 10 minutes, and the chamber was evacuated again to 600 mTorr. Plasma was generated in the post-plasma stage for a period of 2 minutes. In some cases, a different power level was used for the pre-plasma stage than for the post-plasma stage. If two different power levels were used, the first number in the third column of Table 1 is the RF level for the pre-plasma stage, and the second number is the RF level for the post-plasma stage.

Detailed Description Text (48):
After the post-plasma treatment, the chamber was vented to 1 atmosphere, evacuated to a pressure of 600 mTorr, and vented again to 1 atmosphere. No hold was used after the post-plasma vent. The lumens with inoculated coupons were removed from the chamber, and the inoculated coupons were tested for number of survivors/total tested as a measure of the effectiveness of the sterilization treatment.

Detailed Description Text (54):
The cycle of Example 1B was used with four 5 minute pre-plasma treatments with a vent in between the plasma treatments, 6.5 minutes of diffusion after introduction of the hydrogen peroxide, holding the vent during diffusion for 10 minutes, and 2 minutes of post-plasma.

Detailed Description Text (59):
The following experiments demonstrate the benefit of holding the pressure in the chamber at one atmosphere pressure after venting following the post-plasma treatment. The data in the following experiments demonstrate that maintaining the vent pressure at one atmosphere pressure in the vent after the post-plasma stage reduces the residual levels of sterilant on the sterilized instruments.

Detailed Description Text (63):
A segmented polyurethane was cut to defined dimensions was used as the test material. This material is known to be a high absorber of hydrogen peroxide. Sterilization test conditions as in Experiment 1D were used for this residual evaluation, with four 5 minute pre-plasma treatments with a vent in between the plasma treatments, 6.5 minutes of diffusion after introduction of the hydrogen peroxide, holding the vent during diffusion for 10 minutes, and 2 minutes of post-plasma. Additional steps were added after the sterilization steps to evaluate the method for enhancing the residual removal.

CLAIMS:

4. The method of claim 1, wherein said chemical sterilant comprises hydrogen peroxide.

14. The method of claim 13, wherein said chemical sterilant comprises hydrogen peroxide.

24. The method of claim 23, wherein said antimicrobial agent comprises hydrogen peroxide.

L3: Entry 54 of 147 File: USPT Mar 12, 2002

DOCUMENT-IDENTIFIER: US 6355448 B1
**** See image for Certificate of Correction ****
TITLE: Sterilization indicator with chemically stabilized enzyme

Abstract Text (1):
A sterilization indicator for testing the effectiveness of a sterilization procedure comprises a source of an enzyme, a sterilant-resistant chemical associated with the enzyme, and a substrate that reacts with the enzyme to form a detectable enzyme-modified product that provides an indication of the failure of the sterilization procedure. The sterilant-resistant chemical may be a polyglycerol alkyl ester, polyglycerol alkyl ether, an ethoxylated polyhydric alcohol ester, or a polyhydric alcohol ether. The indicator may be used to test the effectiveness of a hydrogen peroxide plasma sterilization procedure and may be provided with a non-challenge test pack or a lumen-challenge test pack.

Brief Summary Text (10):
Premature inactivation of enzyme has also been observed in dual rapid readout indicators that have been exposed to hydrogen peroxide plasma sterilization procedures. Sterilization processes using hydrogen peroxide plasma are known in the art and are described, for example, in U.S. Pat. No. 4,643,876, issued to Jacobs et al. Plasma refers to the portion of the gas or vapors of a sterilant that includes electrons, ions, free radicals, dissociated atoms and molecules that are produced when an electrical field is applied to the sterilant, and includes any radiation produced by the sterilant after application of the electrical field. In hydrogen peroxide plasma sterilization procedures, a vacuum is typically drawn in a sterilization chamber and hydrogen peroxide vapor is injected and allowed to diffuse throughout the chamber and contact the surfaces of all items that are intended to be sterilized. A vacuum is then drawn to remove the hydrogen peroxide vapor, and a plasma is generated within the chamber by an electrical power source, such as a radio frequency (RF) power source. The power is continued for a period of time sufficient to create a plasma that kills any microorganisms within the chamber. The precise mechanism responsible for premature inactivation in hydrogen peroxide plasma sterilization procedures is not known.

Brief Summary Text (18):
In addition, the invention provides a sterilization indicator for specific use in a hydrogen peroxide plasma sterilization procedure in which the enzyme has been chemically treated to enhance its resistance to premature inactivation. The sterilization indicator includes a source of active enzyme, a sterilant-resistant chemical associated with the source of active enzyme, and a substrate that is capable of reacting with the active enzyme to form an enzyme-modified product that provides a detectable indication of the failure of a sterilization procedure. In this embodiment, the sterilant-resistant chemical is preferably selected from the group consisting of decaglyceryl decaoleate, decaglycerol pentaoleate, tetraglycerol monooleate, decaglyceryl tri-oleate, decaglycerol hexaoleate, hexaglycerol dioleate, polyoxyethylene (60) glycerol monostearate, polyoxyethylene (20) sorbitan monostearate, and hexaglyn di-stearate.

Brief Summary Text (19):
In a preferred embodiment, the sterilization indicator for use in hydrogen peroxide plasma procedures is a self-contained biological indicator. The indicator employs a source of active enzyme that has been chemically treated to enhance its resistance to premature inactivation. The self-contained biological indicator comprises a compressible outer container, a breakable inner container, a source of active enzyme associated with a sterilant-resistant chemical, and a substrate that is capable of reacting with the enzyme to form an enzyme-modified product that provides a detectable indication of the failure of a sterilization procedure. The outer container has at

least one opening to allow sterilant to enter the outer container during a sterilization procedure. The inner container is sealed at both ends and contains the reactive substrate. The source of active enzyme is located between the walls of the outer container and the inner container.

Brief Summary Text (20):
The hydrogen peroxide plasma indicators of the invention may be used either alone or as part of a test pack. The invention provides two embodiments of a test pack for use with the sterilization indicators: a non-challenge test pack and a lumen-challenge test pack.

Detailed Description Text (12):
Microorganisms that are particularly preferred to serve as the sources of active enzyme in the indicators of the invention include Bacillus stearothermophilus and Bacillus subtilis, which are microorganisms that are commonly used as test microorganisms in spore outgrowth indicators utilized to monitor sterilization procedures. Where dual rapid readout indicators are used, these microorganisms may serve as both the source of active enzyme in the rapid enzyme test and the test microorganism for the spore outgrowth test. Bacillus stearothermophilus is particularly preferred for monitoring both steam and hydrogen peroxide plasma sterilization procedures. Bacillus subtilis is particularly preferred for monitoring ethylene oxide sterilization procedures and may be used to monitor hydrogen peroxide plasma sterilization procedures. 3M.TM. ATTEST.TM. 1291 and 1292 Rapid Readout Indicators, commercially available from 3M Company, St. Paul, Minn., are dual rapid readout indicators that measure the activity of the enzyme alpha-D-glucosidase, from Bacillus stearothermophilus, and the growth of B. stearothermophilus live spores.

Detailed Description Text (30):
The sterilization indicator of the invention may suitably be used to monitor the effectiveness of any type of sterilization procedure, including sterilization procedures that use steam, hydrogen peroxide vapor phase, hydrogen peroxide plasma, ethylene oxide gas, dry heat, propylene oxide gas, methyl bromide, chlorine dioxide, formaldehyde and peracetic acid (alone or with a vapor phase), and any other gaseous or liquid agents. More preferably, the biological indicator may be used to monitor the effectiveness of any sterilization procedures in which there is a risk that the enzyme will be prematurely inactivated during the sterilization cycle. Sterilization indicators of the invention are most preferably used to monitor the effectiveness of a steam sterilization process utilizing a conditioning phase in which a vacuum is drawn in the chamber before steam is introduced, such as those depicted by the graphs in FIGS. 4 and 5.

Detailed Description Text (31):
In another embodiment of the invention, the sterilization indicator 10 is made specifically for use in monitoring the effectiveness of hydrogen peroxide plasma sterilization procedures, by treating the source of active enzyme with one or more sterilant-resistant chemicals that are especially resistant to premature inactivation during the hydrogen peroxide plasma sterilization procedure. These indicators may be used either alone or as part of a test pack, which includes a tray and a lid in addition to the sterilization indicator. The design of the test pack may be adjusted, as discussed below, to provide the sterilization indicator with a variable amount of additional resistance to the hydrogen peroxide plasma procedure. In one embodiment, the test pack may provide no additional resistance relative to the resistance of the indicator when used alone; and in an alternative embodiment, the test pack may provide the indicator with additional resistance that is equivalent to the additional resistance the indicator would experience if placed within a lumen having a defined cross-sectional area and length.

Detailed Description Text (32):
The sterilization indicators of the invention may be used to monitor the effectiveness of any of the hydrogen peroxide plasma sterilization procedures known in the art, including, for example, the procedures described in U.S. Pat. No. 4,643,876.

Detailed Description Text (33):
In a preferred embodiment of the invention, the hydrogen peroxide plasma indicator of the invention is either an enzyme indicator or a dual rapid readout indicator, as described above, in which the source of active enzyme has been treated with one or more sterilant-resistant chemicals. Suitable sterilant-resistant chemicals include decaglyceryl decaoleate, decaglycerol pentaoleate, tetraglycerol monooleate, decaglyceryl trioleate, decaglycerol hexaoleate, hexaglycerol dioleate, polyoxyethylene

(60) glycerol monostearate, polyoxyethylene (20) sorbitan monostearate and hexaglyn di-stearate.

Detailed Description Text (38):
In a preferred embodiment of the invention, the hydrogen peroxide plasma indicator is a dual rapid readout indicator in which the spores of a microorganism serve as both the source of active enzyme for the enzyme activity test, and the test microorganism for the spore outgrowth test. Suitable microorganisms include Bacillus stearothermophilus and Bacillus subtilis. In the most preferred embodiment, Bacillus stearothermophilus spores are used in the indicators.

Detailed Description Text (39):
The spores for use in hydrogen peroxide plasma indicators are treated with sterilant-resistant chemicals using the procedure detailed above. Cultured spores are removed from culture plates and washed by sequential suspension in water followed by centrifugation. A predetermined number of spores, preferably 1.times.10.sup.6, are then suspended in a solution containing the sterilant-resistant chemical and transferred to the carrier strip 16. A person of ordinary skill in the art will be able to ascertain without undue experimentation the optimal concentrations of the various sterilant-resistant chemicals used in practicing the invention. Accordingly, the invention is not limited to the use of the identified chemicals at any specific concentration or range of concentrations. However, the preferred concentrations of the sterilant-resistant chemicals for use in hydrogen peroxide plasma sterilization procedures are as follows:

Detailed Description Text (40):
Sterilization indicators for use with hydrogen peroxide plasma procedures are preferably prepared according to the methods discussed above and have the configuration of the indicator 10 shown in FIG. 1. However, when the indicator is to be used to monitor hydrogen peroxide plasma procedures, closure member 22 is preferably made of a high-density fiber material, such as TYVEK.TM. high-density polyethylene fiber material, commercially available from E.I. du Pont de NeMours and Co., Wilmington, Del.

Detailed Description Text (41):
In use, the sterilization indicator 10 is placed in the sterilization chamber and exposed to a hydrogen peroxide plasma sterilization procedure. Sterilant enters the indicator 10 through vent 28 and closure member 22, and contacts the source of active enzyme located on enzyme carrier 16. After the procedure is completed, the indicator 10 is removed from the sterilization chamber and the sides of the outer tube 12 are compressed, breaking the frangible inner tube 18 and releasing the enzyme substrate so that it may contact the source of enzyme on carrier strip 16. The sterilization indicator 10 is then incubated for a period of time sufficient for any active enzyme remaining in the indicator to react with the substrate and form an enzyme-modified product, which provides a detectable indication of the failure of the sterilization procedure. The enzyme-modified product may be detectable as fluorescence, luminescence or a color change. If the sterilization procedure is effective and all active enzyme has been inactivated, then no detectable signal is generated upon incubation.

Detailed Description Text (42):
In a more preferred embodiment of the sterilization indicator 30 for use in a hydrogen peroxide plasma sterilization procedure, shown in FIGS. 6-7, the enzyme carrier 36 is located within outer tube 12 near the closed end of the tube, and a barrier 38 is situated between the carrier strip 36 and the inner tube 18. The barrier is preferably a disc of polypropylene blown microfiber material having a weight of 200 g/sq. meter, commercially available as "THINSULATE.TM. 200-B brand Thermal Insulation" from 3M Company, St. Paul, Minn.

Detailed Description Text (47):
Both the tray 42 and the lid 50 of the non-challenge test pack 40 are preferably made of plastic materials that are thermally-resistant and that do not retain residual sterilant following a sterilization procedure. As used herein, the term "thermally resistant" means capable of withstanding the maximum temperature achieved in a particular sterilization procedure without deformation, shrinkage, melting or decomposition. The maximum temperature achieved during a sterilization procedure varies depending on the type of sterilization procedure that is being used. For example, many steam sterilization procedures are carried out at temperatures of 121.degree. C. or higher, whereas hydrogen peroxide plasma sterilization procedures are commonly performed at temperatures of less than 60.degree. C. In selecting the proper

thermally-resistant plastic for use in a tray, these temperature differences between the various sterilization procedures must properly be taken into consideration and a plastic should be selected with a glass transition temperature above the maximum temperature of the sterilization procedure in which the indicator will be used.

Detailed Description Text (48):
In a preferred embodiment of the non-challenge test pack, suitable for use in hydrogen peroxide plasma sterilization procedures, the tray is made of polyethylene terephthalate with a glycol additive (PETG). Other examples of suitable thermally-resistant plastics for used in test pack tray 42 include polyvinyl chloride, polyethylene, ultra-high molecular weight polyethylene, polyetheramide, polysulfones, chorotrifluoroethylene, polyvinylfluoride, polytetrafluoroethylene (PTFE), polypropylene, polystyrene, and polyesters.

Detailed Description Text (49):
The lid 50 may be made of the same material as the tray 42. Preferably the lid 20 is made of a plastic material that is translucent or transparent. In the most preferred embodiment, suitable for use in hydrogen peroxide plasma sterilization procedures, the lid 50 is made of a transparent film and is heat sealed to the rim surface 44. An example of a suitable transparent film is a polyester film coated with a blend of polyethylene and ethylene vinylacetate, commercially available as SCOTCHPAK.TM. Polyester Film from 3M Company, St. Paul, Minn.

Detailed Description Text (52):
The lumen path 70 has a defined length and cross-sectional area. The dimensions of the lumen path may be selected or adjusted to duplicate the conditions in a lumen having known dimensions. In a preferred embodiment of the test pack, which may preferably be used to test the effectiveness of a hydrogen peroxide plasma sterilization procedure, the lumen path is about approximately twelve inches (30.48 cm) long and has a cross-sectional area that is about the area of a circle having a diameter of 0.25 inches (0.635 cm). However, any lumen length and cross-sectional area may be chosen, and all are considered to be within the scope of the invention. FIG. 10, for example, shows an alternative embodiment of the lumen-challenge test pack 80 in which the lumen path has a different length than the lumen path 70 shown in FIG. 8.

Detailed Description Text (54):
The tray 72 and the lid 68 are made of thermally-resistant plastic materials that should be selected in the manner described above with regard to the non-challenge test pack. In a preferred embodiment suitable for use in hydrogen peroxide plasma procedures, the tray 72 is made of polyethylene terephthalate with a glycol additive (PETG) and the lid is made of a transparent film comprising a blend of polyethylene and ethylene vinylacetate, commercially available as SCOTCHPAK.TM. Polyester Film from 3M Company, St. Paul, Minn. The film 68 may be heat-sealed to the tray 72.

Detailed Description Text (57):
Examples 1-5 report the results of tests to determine whether sterilization indicators prepared with spores that have been treated with the chemicals listed in Tables 1-5 demonstrate increased resistance to premature inactivation of enzyme in prevacuum steam sterilization cycles. Examples 6-9 report the results of tests to determine whether sterilization indicators prepared with spores that have been treated with the chemicals listed in Tables 6-9 demonstrate increased resistance to premature inactivation of enzyme in hydrogen peroxide plasma sterilization procedures. Example 10 reports the results of tests that demonstrate the effectiveness of the non-challenge test pack and the lumen-challenge test pack of the invention.

Detailed Description Text (94):
This Example reports the results of an experiment to determine whether enzymes associated with spores that have been treated with the chemicals listed in Table 6 are more resistant to premature inactivation in hydrogen peroxide plasma sterilization procedures than enzymes associated with untreated spores.

Detailed Description Text (95):
Sterilization indicators were made as described above with spores that had been coated with each of the chemicals and concentrations listed in Table 6. The indicators were placed in instrument trays and exposed to a hydrogen peroxide plasma sterilization procedure at 45-55.degree. C. in a STERRAD.TM. 100SI GMP Sterilizer, obtained from Advanced Sterilization Products Co., Irvine, Calif. During the sterilization procedure a vacuum was drawn in the sterilization chamber for 5-6 minutes until the pressure was reduced to 300 mTorr. A 1.8 ml aliquot of an aqueous solution of 58-60% hydrogen

peroxide was then injected into the sterilization chamber over a period of about 6 minutes, yielding an empty chamber concentration of 6-7 mg/ml hydrogen peroxide, and hydrogen peroxide vapor was allowed to diffuse throughout the chamber for 1-22 minutes at 6-10 Torr. A vacuum was then drawn, reducing the pressure to 500 mTorr and removing all detectable hydrogen peroxide vapor from the chamber. A plasma phase was then generated in the chamber by emitting an RF power source at 400 watts and 13.56 Mflz for about 15-16 minutes at 500 mTorr, after which the chamber was vented for 3-4 minutes until atmospheric pressure was reached in the chamber.

Detailed Description Text (98):
The data in Table 6 indicates that the accuracy of the sterilization indicators is improved in hydrogen peroxide plasma sterilization procedures, 1-3 hours after exposure, compared to indicators made with untreated spores, when the indicators are prepared with spores that have been treated with decaglyceryl decaoleate, decaglycerol pentaoleate, tetraglycerol monooleate, decaglycerol hexaoleate, and 1,2,3-Propantrial. It can be inferred from the data that treatment with these chemicals increases the resistance of the enzyme to premature inactivation in hydrogen peroxide plasma sterilization procedures.

Detailed Description Text (101):
This Example reports the results of an experiment to determine whether enzymes associated with spores that have been treated with the chemicals listed in Table 7 are more resistant to premature inactivation in hydrogen peroxide plasma sterilization procedures than enzymes associated with untreated spores.

Detailed Description Text (102):
Sterilization indicators were made as described above with spores that had been coated with each of the chemicals and concentrations listed in Table 7. The indicators were placed in instrument trays and exposed to a hydrogen peroxide plasma sterilization procedure at 45-55.degree. C. in a STERRAD.TM. 100SI GMP Sterilizer, obtained from Advanced Sterilization Products Co., Irvine, Calif. During the sterilization procedure a vacuum was drawn in the sterilization chamber for 5-6 minutes until the pressure was reduced to 300 mTorr. A 1.8 ml aliquot of an aqueous solution of 58-60% hydrogen peroxide was then injected into the sterilization chamber over a period of about 6 minutes, yielding an empty chamber concentration of 6-7 mg/ml hydrogen peroxide, and hydrogen peroxide vapor was allowed to diffuse throughout the chamber for 1-22 minutes at 6-10 Torr. A vacuum was then drawn, reducing the pressure to 500 mTorr and removing all detectable hydrogen peroxide vapor from the chamber. A plasma phase was then generated in the chamber by emitting an RF power source at 400 watts and 13.56 MHz for about 15-16 minutes at 500 mTorr, after which the chamber was vented for 3-4 minutes until atmospheric pressure was reached in the chamber.

Detailed Description Text (105):
The data in Table 7 indicates that the accuracy of sterilization indicators is improved in hydrogen peroxide plasma sterilization procedures, 2-3 hours after exposure, compared to indicators made with untreated spores, when the indicators are prepared with spores that have been treated with decaglyceryl decaoleate, POE (60) glycerol monostearate and POE (20) sorbitan monostearate. It can be inferred from the data that treatment with these chemicals increases the resistance of the enzyme to premature inactivation in hydrogen peroxide plasma sterilization procedures.

Detailed Description Text (108):
This Example reports the results of an experiment to determine whether enzymes associated with spores that have been treated with the chemicals listed in Table 8 are more resistant to premature inactivation in hydrogen peroxide plasma sterilization procedures than enzymes associated with untreated spores.

Detailed Description Text (109):
Sterilization indicators were made as described above with spores that had been coated with each of the chemicals and concentrations listed in Table 8. The indicators were placed in instrument trays and exposed to a hydrogen peroxide plasma sterilization procedure at 45-55.degree. C. in a STERRAD.TM. 100SI GMP Sterilizer, obtained from Advanced Sterilization Products Co., Irvine, Calif. During the sterilization procedure a vacuum was drawn in the sterilization chamber for 5-6 minutes until the pressure was reduced to 300 mTorr. A 1.8 ml aliquot of an aqueous solution of 58-60% hydrogen peroxide was then injected into the sterilization chamber over a period of about 6 minutes, yielding an empty chamber concentration of 6-7 mg/ml hydrogen peroxide, and hydrogen peroxide vapor was allowed to diffuse throughout the chamber for 1-22 minutes at 6-10 Torr. A vacuum was then drawn, reducing the pressure to 500 mTorr and removing

all detectable hydrogen peroxide vapor from the chamber. A plasma phase was then generated in the chamber by emitting an RF power source at 400 watts and 13.56 MHz for about 15-16 minutes at 500 mTorr, after which the chamber was vented for 3-4 minutes until atmospheric pressure was reached in the chamber.

Detailed Description Text (112):
The data in Table 8 indicates that the accuracy of sterilization indicators is improved in hydrogen peroxide plasma sterilization procedures, 1-3 hours after exposure, compared to indicators made with untreated spores, when the indicators are prepared with spores that have been treated with hexaglyn di-stearate. It can be inferred from the data that treatment with this chemicals increases the resistance of the enzyme to premature inactivation in hydrogen peroxide plasma sterilization procedures.

Detailed Description Text (115):
This Example reports the results of an experiment to determine the effective concentration range of decaglyceryl decaoleate for use in treating spores to prevent premature inactivation enzymes associate with the spores in hydrogen peroxide plasma sterilization procedures than enzymes in untreated spores.

Detailed Description Text (116):
Sterilization indicators were made as described above with spores that had been coated with decaglyceryl decaoleate at each of the concentrations listed in Table 9. The indicators were placed in instrument trays and exposed to a hydrogen peroxide plasma sterilization procedure at 45-55.degree. C. in a STERRAD.TM. 100SI GMP Sterilizer, obtained from Advanced Sterilization Products Co., Irvine, Calif. During the sterilization procedure a vacuum was drawn in the sterilization chamber for 5-6 minutes until the pressure was reduced to 300 mTorr. A 1.8 ml aliquot of an aqueous solution of 58-60% hydrogen peroxide was then injected into the sterilization chamber over a period of about 6 minutes, yielding an empty chamber concentration of 6-7 mg/ml hydrogen peroxide, and hydrogen peroxide vapor was allowed to diffuse throughout the chamber for 1-22 minutes at 6-10 Torr. A vacuum was then drawn, reducing the pressure to 500 mTorr and removing all detectable hydrogen peroxide vapor from the chamber. A plasma phase was then generated in the chamber by emitting an RF power source at 400 watts and 13.56 MHz for about 15-16 minutes at 500 mTorr, after which the chamber was vented for 3-4 minutes until atmospheric pressure was reached in the chamber.

Detailed Description Text (119):
The data in Table 9 indicates that the accuracy of sterilization indicators is improved in hydrogen peroxide plasma sterilization procedures, 2-3 hours after exposure, compared to indicators made with untreated spores, when the indicators are prepared with spores that have been treated with decaglyceryl decaoleate at concentrations of 5-100 mg/ml Decaglyceryl decaoleate was obtained from Lonza, Inc., Fairlawn, N.J.

Detailed Description Text (121):
This Example reports the results of an experiment to determine whether the lumen-challenge test pack of the invention increases the resistance of a sterilization indicator within the test pack to a hydrogen peroxide plasma sterilization procedure.

Detailed Description Text (122):
Lumen-challenge test packs made according to the invention were exposed to partial and full cycles of a hydrogen peroxide plasma procedure, along with non-challenge test packs made according to the invention, a laboratory lumen-challenge device, and a sterilization indicator exposed without a test pack. The lumen-challenge test packs and the non-challenge test packs used in the Example included a sterilization indicator prepared as described above, with spores that had been treated with decaglycerol decaoleate at 5 mg/ml. The experimental lumen-challenge device included a carrier strip that was identical to the carrier strip in the sterilization indicators used in the test packs. The results of the experiment are reported in Table 10.

Detailed Description Text (127):
One set of devices was placed in an instrument tray and exposed to a full cycle of a hydrogen peroxide plasma sterilization procedure at 45-55.degree. C. in a STERRAD.TM. 100SI GMP Sterilizer, obtained from Advanced Sterilization Products Co., Irvine, Calif. During the sterilization procedure a vacuum was drawn in the sterilization chamber for 5-6 minutes until the pressure was reduced to 300 mTorr. A 1.8 ml aliquot of an aqueous solution of 58-60% hydrogen peroxide was then injected into the sterilization chamber over a period of about 6 minutes, yielding an empty chamber concentration of 6-7 mg/ml hydrogen peroxide, and hydrogen peroxide vapor was allowed to diffuse throughout the chamber for 44 minutes at 6-10 Torr. A vacuum was then drawn, reducing the pressure to

500 mTorr and removing all detectable hydrogen peroxide vapor from the chamber. A plasma phase was then generated in the chamber by emitting an RF power source at 400 watts and 13.56 MHz for about 15-16 minutes at 500 mTorr, after which the chamber was vented for 3-4 minutes until atmospheric pressure was reached in the chamber.

Detailed Description Text (128):
A second set of devices was placed in an instrument tray and exposed to a partial cycle of a hydrogen peroxide plasma sterilization procedure at 45-55.degree. C. in the STERRAD.TM. 100SI GMP Sterilizer. In the partial cycle, hydrogen peroxide vapor was allowed to diffuse throughout the chamber for only 9 minutes, as compared to the much longer period of diffusion in the full cycle. Otherwise the partial cycle and the full cycle were the same.

Detailed Description Text (131):
The fractional cycle data in Table 10 indicates that the six inch, nine inch and twelve inch lumen-challenge test packs of the invention provide a challenge to hydrogen peroxide plasma sterilization procedures that is greater than the challenge provided by sterilization indicators exposed without the test packs, and that the non-challenge test pack of the invention provides a challenge that is equivalent to that of a sterilization indicator exposed without a test pack.

Other Reference Publication (25):
Alfa et al., "Comparison of Ion Plasma, Vaporized Hydrogen Peroxide, and 100% Ethylene Oxide Sterilizers to the 12/88 Ehtylene Oxide Gas Sterilizer", Infection Control and Hospital Epidemiology, vol. 17, No. 2, Feb. 1996, pp. 92-100.

Other Reference Publication (26):
Mecke, "Hydrogen Peroxide Plasma--an Interesting Microbiocidal Concept", Hygiene+Medizin, 1992:17:pp.537-543.

L3: Entry 79 of 147 File: USPT May 9, 2000

DOCUMENT-IDENTIFIER: US 6060019 A
TITLE: Plasma-enhanced vacuum drying

Abstract Text (1):
A plasma-enhanced vacuum drying method is disclosed. It is advantageously applied in plasma sterilization processes in particular, and represents a significant improvement for general evacuation drying methods. Articles to be sterilized are placed in a sealed chamber and the chamber is evacuated. A plasma of residual gas species is generated in the chamber during an initial evacuation step. This promotes drying of the articles and advantageously allows a desired pressure to be attained more quickly than without the plasma. Sterilizing gas is injected into the chamber, and a second plasma is generated to activate the sterilizing gas plasma, thereby sterilizing the articles in the chamber.

Brief Summary Text (4):
Some new commercial systems for sterilizing medical instruments and the like utilize low-temperature reactive gas plasma to achieve rapid, low-temperature, low-moisture sterilization of medical items. Low-temperature gas plasma is sometimes described as a reactive cloud which may contain ions, electrons, and/or neutral atomic particles. This state of matter can be produced through the action of electric or magnetic fields, or through other external forces such as high-energy particle flux. In general, an electric field can be in any frequency range (An example of a naturally occurring plasma is the aurora borealis or the northern lights). One commercial embodiment of plasma sterilization is the STERRAD.RTM. Sterilization Process practiced by the assignee of the present application. The STERRAD.RTM. process is performed in the following manner. The items to be sterilized are placed in the sterilization chamber, the chamber is closed, and a vacuum is drawn. An aqueous solution of hydrogen peroxide is injected and vaporized into the chamber so that it surrounds the items to be sterilized. After reduction of the pressure in the sterilization chamber, a low-temperature gas plasma is initiated by applying radio frequency energy to create an electrical field. In the plasma, the hydrogen peroxide vapor is dissociated into reactive species that collide/react with and kill microorganisms. After the activated components react with the organisms or with each other, they lose their high energy and recombine to form oxygen, water, and other nontoxic byproducts. The plasma is maintained for a sufficient time to achieve sterilization and remove residuals. At the completion of the process, the RF energy is turned off, the vacuum is released, and the chamber is returned to atmospheric pressure by the introduction of High Efficiency Particulate-filtered Air (HEPA).

Brief Summary Text (11):
According to the present invention, a method is provided for sterilizing an object in which the item to be sterilized is first placed in a sealed chamber. A vacuum is then applied to the chamber. At a first predetermined vacuum pressure, a plasma is generated in the chamber. This first plasma enhances the drying of the item to be sterilized by transferring energy to any ice or water which may be present inside the sterilizer, thereby promoting vaporization with evacuation. Preferably, the plasma generated at the first pressure is terminated after a period of time which is proportional to the quantity of wetting agent present. The vacuum is further applied to reach a second predetermined vacuum pressure which is lower than the first pressure. Finally, a sterilizing gas is injected into the chamber and radio frequency or other energy may be applied to generate a plasma with the sterilizing gas. After a sufficient time has elapsed for the item to be completely sterilized, the chamber is vented to atmospheric pressure and the article is removed.

Brief Summary Text (12):
According to another aspect of the present invention, the first predetermined vacuum

pressure is approximately 700 mTorr, and the second predetermined level is approximately 300 mTorr. While the plasma is being generated, the vacuum continues to be drawn until a pressure of approximately 300 mTorr has been reached. Alternatively, the RF generator may be engaged for a predetermined period of time, after which the RF generator is switched off while continuing to evacuate the chamber. When the second predetermined level has been reached, a reactive fluid such as hydrogen peroxide is introduced into the sterilizer. The fluid is allowed to diffuse throughout the sterilizer for a number of minutes and then a second vacuum is drawn inside the sterilizer. When a vacuum of approximately 500 mTorr has been reached, the RF generator is then energized for a second time. In the plasma sterilization apparatus, the RF energy initiates a plasma of the remaining air molecules and molecules of the sterilizing gas transforming them into a number of highly reactive species. These reactive species attack any micro organism present in the chamber, inactivating them. After the RF generator has been engaged for a sufficient time and the sterilization process is complete, the RF generator is turned off and the vacuum is vented to atmospheric pressure through a suitable filter.

Detailed Description Text (2):
Referring to the drawings, FIG. 1 depicts a plasma sterilizer in block diagram form generally at 10. The sterilizer 10 and its components and methods of use are described more fully in U.S. Pat. No. 4,756,882, issued Jul. 12, 1988 and assigned to the assignee of the present application. This patent is incorporated by reference herein. The sterilizer includes a vacuum and plasma chamber 11; a vacuum pump 12 connected to the electrode 11 by a valve 17; and a source of suitable reactive agent 13 such as hydrogen peroxide and connected to the vacuum chamber 11 by a line having a valve 19 therein. The sterilizer 10 also includes an RF generator 14 electrically connected to the plasma generator inside the vacuum chamber 11 by a suitable coupling 18, as well as a HEPA vent 15 connected to the vacuum chamber via a line and a valve 41. A process control logic 16, preferably a programmable computer, is connected to each of the components which are connected to the vacuum chamber 11. The process control logic 16 directs the operation of each of the components connected to the vacuum chamber at the appropriate time to effectuate the sterilization operation.

Detailed Description Text (3):
The vacuum chamber 11 contains the objects to be sterilized and is sufficiently gas-tight to support a vacuum of less than 300 mTorr. Inside the chamber 11 is an RF antenna, or electrode array 27 to which the RF energy is supplied. In a preferred embodiment the electrode is arranged such that it is tubuler and equidistant from the chamber 11 wall to produce a symmetric RF electric field distribution. The electrode excites a plasma when an RF potential is applied by the RF generator 14 through the RF coupling 18. The RF coupling 18 may be a coaxial cable or other such waveguide capable of transmitting high power RF energy without significant impedance loss connected to an impedance matching device for the electrode.

Detailed Description Text (6):
Operation of the plasma sterilizer 10 without the plasma-enhanced drying technique of the present invention is described in schematic form in FIGS. 2 and 3, which respectively illustrate the sequence of operations employed by the sterilizer 10 and the corresponding pressure in chamber 11 as a function of time.

Detailed Description Text (11):
Generating the plasma induces a brief rise in pressure, as indicated by the pressure immediately after step 28. The plasma generator remains energized for approximately 15 minutes during the sterilization step 30, and the plasma it creates can effectively destroy any pathogens present in the vacuum chamber 11. The sterilization process is conducted at an approximately constant pressure of 500 mTorr, as indicated by curve 31 in FIG. 3.

Detailed Description Text (14):
After the articles to be sterilized are introduced into the chamber 11 and the chamber 11 is sealed, the vacuum pump 12 and valve 17 are energized to evacuate the chamber 11 to a predetermined pressure, in this case a pressure of about 700 mTorr, as indicated by step 40 in FIG. 5. The chamber pressure generally behaves as shown by curve 50 of FIG. 6. When the desired pressure has been reached, the process control logic 16 transmits a command to the RF generator 14 to energize the electrode within the chamber 11, as indicated by step 42. This action causes a gas plasma to be created inside the chamber 11 comprised of residual gas species. It will be appreciated that other chamber and electrode configurations as well as RF generators may render appreciable variation in the pressure range over which a plasma may be supported. Moreover, various other

conditions such as solvent content, process time, temperature and equilibrium vapor pressure will determine the conditions under which plasma enhancement is most desirable. In the present embodiments herein disclosed the plasma tranfers energy to the condensed water thereby aiding the vaporization process. While such energy transfer serves to increase the water temperature, it is preferred that the plasma does not chemically or physically alter the load surfaces as is commonly encountered in a sputtering or plasma chemical process. Thus, the plasma should preferably have average energy and momentum characteristics sufficient to impart heat energy to the condensed water, while leaving the load surface molecules and molecular bonds intact. In the present embodiment, the plasma is usually generated when the chamber pressure is approximately 700 mTorr, whereas at higher pressures such generation may be limited due to the impedance between the chamber 11 and the RF generator 14. Furthermore, plasma generation at about 700 mTorr substantially minimizes the total process time required to reach a pre-sterilization pressure of 300 mTorr.

Detailed Description Text (17):
As shown in FIG. 4, the plasma-enhanced drying technique of the present invention substantially decreases the time required for the vacuum pump 12 to reduce the chamber pressure required for the operation of the sterilizer 10. Performance curves 54 and 56 represent the chamber pressure as a function of time during evacuation for representative loads with and without a plasma-enhanced vacuum drying process respectively. FIG. 8 is a plot of evacuation performance for evacuation after plasma-enhancement 82 and without plasma enhancement 80 as the chamber pressure approaches a nominal final pressure of about 300 mTorr. Indeed, as shown in FIG. 8, the evacuation rate after plasma excitation, curve 82, is considerably higher than by vacuum evacuation alone, curve 80. A comparison of these data indicates that the performance gain realized through use of plasma-enhanced drying is substantial. The present invention achieves this result because the plasma generated during step 42 transfers energy from the RF generator to the liquid present in the chamber. The energy transferred to the liquid promotes vaporization and hence speeds the drying process.

Detailed Description Text (18):
This gain in performance represents an increase in the effective pump efficiency during the initial evacuation/drying stages 40-48, and results in faster, more consistent operation of the sterilizer 10. It has been found that plasma-enhanced drying is most useful when the time taken by the vacuum pump 12 to reach a pressure of 1 Torr during stage 40 is between 5 and 9 minutes. If this time is less than 5 minutes, the items in the chamber are already reasonably dry and plasma-enhanced drying may not greatly speed up the drying process. If, on the other hand, this time is greater than 9 minutes, the items in the chamber may be too wet to process by the sterilizer as presently constituted. The values disclosed herein are valid for the particular configuration of the current embodiment. However, these values may differ substantially to maximize the benefit of the invention for other configurations. It has been determined in practice that application of the plasma for a duration of time proportional to the wetness of the objects in the chamber results in optimum drying of the materials placed therein. However, durations longer than 15 minutes have been found to decrease the chance of reaching the desired pre-sterilization pressure of 300 mTorr inside the chamber 11 within the desired 20 minute duration (the maximum time presently allowed in a commercial embodiment of the sterilizer 10) of initiation of the vacuum pumping step 40.

CLAIMS:

1. A vacuum sterilization method, comprising:

placing into a chamber an article to be sterilized, said article having a quantity of condensed residue thereon to be evaporated, wherein said condensed residue comprises water;

evacuating the chamber to reach a pressure selected to facilitate evaporation of said residue, and leaving a residual gas in said chamber;

generating a gas plasma in the chamber at said pressure from said residual gas;

maintaining the gas plasma in the chamber for a duration sufficient to evaporate a substantial portion of the condensed residue; and

introducing a sterilizing gas comprising hydrogen peroxide into the chamber subsequent to evaporation of the substantial portion of the condensed residue at a pressure

selected to facilitate sterilization.

6. The method of claim 1, further comprising generating plasma after introducing said sterilizing gas comprising hydrogen peroxide.

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L3: Entry 81 of 147 File: USPT Feb 29, 2000

DOCUMENT-IDENTIFIER: US 6030579 A
TITLE: Method of sterilization using pretreatment with hydrogen peroxide

Abstract Text (1):
A method for hydrogen peroxide vapor sterilization of medical devices and similar instruments having long narrow lumens or diffusion restricted areas includes the step of pretreating the article to be sterilized with a dilute solution of hydrogen peroxide prior to exposure to a vacuum or a vacuum followed by plasma. The method is such that, upon vaporization of the solution caused by the vacuum, the hydrogen peroxide remains in contact with the article for a time sufficient to achieve sterilization.

Brief Summary Text (3):
This invention relates to a process for using hydrogen peroxide and negative pressure to sterilize articles such as medical instruments, and more particularly, to a method which includes the step of pretreating the articles with liquid hydrogen peroxide prior to exposure to negative pressure or negative pressure combined with plasma.

Brief Summary Text (6):
Sterilization using liquid hydrogen peroxide solution has been found to require high concentration of sterilant, extended exposure time and/or elevated temperatures. However, sterilization using hydrogen peroxide vapor has been shown to have some advantages over other chemical sterilization processes (see, e.g., U.S. Pat. Nos. 4,169,123 and 4,169,124). The combination of hydrogen peroxide with a plasma provides certain additional advantages, as disclosed in U.S. Pat. No. 4,643,876, issued Feb. 17, 1987 to Jacobs et al. U.S. Pat. No. 4,756,882, issued Jul. 12, 1988 also to Jacobs et al. discloses the use of hydrogen peroxide vapor, generated from an aqueous solution of hydrogen peroxide, as a precursor of the reactive species generated by a plasma generator. The combination of hydrogen peroxide vapor diffusing into close proximity with the article to be sterilized and plasma acts to sterilize the articles, even within closed packages. Further, these methods of combining hydrogen peroxide vapor with a plasma, while useful in "open" systems, have been found to be inadequate to effect sterilization in articles having diffusion-restricted areas, since the methods are dependent upon diffusion of the sterilant vapor into close proximity with the article before sterilization can be achieved. Thus, these methods have been found to require high concentration of sterilant, extended exposure time and/or elevated temperatures when used on long, narrow lumens. For example, lumens longer than 27 cm and/or having an internal diameter of less than 0.3 cm have been particularly difficult to sterilize. Thus, no simple, safe, effective method of sterilizing smaller lumens exists in the prior art.

Brief Summary Text (7):
The sterilization of articles containing diffusion-restricted areas, such as long narrow lumens, therefore presents a special challenge. Methods that use hydrogen peroxide vapor that has been generated from an aqueous solution of hydrogen peroxide have certain disadvantages, because:

Brief Summary Text (8):
1. Water has a higher vapor pressure than hydrogen peroxide and will vaporize faster than hydrogen peroxide from an aqueous solution.

Brief Summary Text (9):
2. Water has a lower molecular weight than hydrogen peroxide and will diffuse faster than hydrogen peroxide in the vapor state.

Brief Summary Text (10):
Because of this, when an aqueous solution of hydrogen peroxide is vaporized in the area

surrounding the items to be sterilized, the water reaches the items first and in higher concentration. The water vapor therefore becomes a barrier to the penetration of hydrogen peroxide vapor into diffusion restricted areas, such as small crevices and long narrow lumens. One cannot solve the problem by removing water from the aqueous solution and using more concentrated hydrogen peroxide, since, among other reasons, concentrated solutions of hydrogen peroxide greater than 65% by weight can be hazardous due to the oxidizing nature thereof.

Brief Summary Text (11):
U.S. Pat. No. 4,952,370 to Cummings et al. discloses a sterilization process wherein aqueous hydrogen peroxide vapor is first condensed on the article to be sterilized, and then a source of vacuum is applied to the sterilization chamber to evaporate the water and hydrogen peroxide from the article. This method is suitable to sterilize surfaces, however, it is ineffective at rapidly sterilizing diffusion-restricted areas, such as those found in lumened devices, since it too depends on the diffusion of the hydrogen peroxide vapor into the lumen to effect sterilization.

Brief Summary Text (12):
U.S. Pat. No. 4,943,414, entitled "Method for Vapor Sterilization of Articles Having Lumens," and issued to Jacobs et al., discloses a process in which a vessel containing a small amount of a vaporizable liquid sterilant solution is attached to a lumen, and the sterilant vaporizes and flows directly into the lumen of the article as the pressure is reduced during the sterilization cycle. This system has the advantage that the water and hydrogen peroxide vapor are pulled through the lumen by the pressure differential that exists, increasing the sterilization rate for lumens, but it has the disadvantage that the vessel needs to be attached to each lumen to be sterilized. In addition, water is vaporized faster and precedes the hydrogen peroxide vapor into the lumen.

Brief Summary Text (16):
One aspect of the present invention relates to a method for sterilizing an interior of a device with a diffusion restricted area, such as a device having a lumen. The method includes the steps of contacting the interior of the device with a liquid solution comprising hydrogen peroxide, and exposing the device to negative pressure for a time period sufficient to effect complete sterilization. In one embodiment, the liquid solution is peracetic acid. If the exposing step is conducted for 1 hour at 40.degree. C. and 10 torr, the diffusion restricted area preferably retains 0.17 mg/L or more hydrogen peroxide, or retains 17% or more of the hydrogen peroxide placed therein after the exposing step. In certain preferred embodiments, the diffusion-restricted area has the same or more diffusion restriction than provided by a lumen 27 cm in length and an internal diameter of 3 mm, or has the same or more diffusion restriction than provided by a lumen having a ratio of length to internal diameter greater than 50. The solution is preferably at a concentration of less than 25% by weight. The contacting step can be performed by delivery via a method such as injection, static soak, liquid flow-through or aerosol spray. In a preferred embodiment, the diffusion-restricted area is a lumen at least 27 cm in length and having an internal diameter of no more than 3 mm, more preferably having an internal diameter of no more than 1 mm. The exposing step is preferably performed for 60 minutes or less, and is preferably performed at a pressure less than the vapor pressure of hydrogen peroxide. Thus, the preferred pressure range under conditions of the present invention is between 0 and 100 torr. In one particularly preferred embodiment, the pressure is approximately 10 torr and the exposing step is conducted at a temperature of approximately 23.degree. C. to approximately 28.degree. C. The exposing step can include the step of heating the article, such as by heating the chamber in which the exposing step occurs. The chamber can be heated to about 40.degree. C. to about 45.degree. C. Alternatively, the solution can be heated, such as to a temperature of about 40.degree. C. to about 45.degree. C. Optionally, the step of exposing the device to a plasma can be conducted during the step of exposing the device to negative pressure. In one embodiment employing exposure to plasma, the method is performed within a first chamber and the plasma is generated in a second, separate chamber. This embodiment further comprises the step of flowing the plasma into the first chamber. Advantageously, the contacting and/or exposing steps of the method can be repeated one or more times.

Brief Summary Text (17):
Another aspect of the present invention relates to a method for sterilizing an interior and an exterior of an article. This method includes the following steps: contacting the article with a liquid solution comprising hydrogen peroxide; and placing the article in a diffusion-restricted environment. The contacting and placing steps can be performed in either order. These steps are followed by exposing the diffusion-restricted

environment to negative pressure for a time period sufficient to effect complete sterilization. The contacting step can be performed both before and after the placing step. If the exposing step is conducted at 40.degree. C. and 10 torr, the diffusion restricted environment preferably retains 0.17 mg/L or more hydrogen peroxide after the exposing step, or retains 17% or more of the hydrogen peroxide placed therein after the exposing step. The exposing step can include the step of heating the article, such as by heating the chamber in which the exposing step occurs or by heating the liquid solution. In certain preferred embodiments, the diffusion-restricted environment has the same or more diffusion restriction than provided by a single entry/exit port of 9 mm or less in internal diameter and 1 cm or greater in length, or is sufficiently diffusion restricted to completely sterilize a stainless steel blade within a 2.2 cm by 60 cm glass tube having a rubber stopper with a 1 mm by 50 cm stainless steel exit tube therein at a vacuum of 10 torr for one hour at 40.degree. C. The solution can be peracetic acid. The contacting step can be by delivery via a method such as injection, static soak, liquid flow-through or aerosol spray. Plasma can also be used during the step of exposing the lumen to negative pressure. If plasma is used, the method can be performed within a sealed chamber and the plasma generated within the container. Thus, the method can be performed within a first chamber and the plasma generated in a second, separate chamber and the plasma flowed into the first chamber. The diffusion-restricted container can have at least one exit tube, such as one that is at least 1.0 cm in length and has an internal diameter of 9 mm or less. The exit tube can also include a filter. In a preferred embodiment, the filter is sufficient to prevent entry of bacteria from the environment into the container. The solution can be used at a concentration of less than 25% by weight. The exposing step is preferably performed for 60 minutes or less. The method can be conducted along with the step of heating the article during the exposing step. Thus, the exposing step can be conducted within a chamber, and the chamber heated during the exposing step. The exposing step can be conducted at a negative pressure between 0 and 100 Torr. Advantageously, the various steps of this method can also be repeated one or more times.

Brief Summary Text (18):
Still one more aspect of the invention relates to a method for making a sterilized article within a diffusion-restricted container. This method includes contacting the article with a solution comprising hydrogen peroxide, and placing the article in the diffusion-restricted container in either order. If the initial contacting step precedes the placing step, the contacting step can be repeated after the placing step. These steps are followed by exposing the diffusion-restricted container to negative pressure for a time period sufficient to effect complete sterilization of the article. The container used in this aspect of the invention has at least one exit tube. The exit tube preferably has a filter therein which is preferably sufficient to prevent entry of bacteria into the container. The exit tube is at least 1.0 cm in length and/or has an internal diameter of 9 mm or less. The solution used can be peracetic acid. Advantageously, the exposing step, the contacting step, or the entire method can be repeated one or more times. In a preferred embodiment, the contacting step comprises delivery via injection, static soak, liquid flow-through or aerosol spray. The container can be exposed to a plasma during the step of exposing the container to negative pressure. In one embodiment, the method is performed within a sealed chamber and the plasma is generated within the chamber. The exposing step is preferably performed for 60 minutes or less and/or at a pressure between 0 and 100 Torr. The container can be heated during the exposing step, or the solution heated prior to the contacting step. The invention also includes the sterilized article within a diffusion-restricted container produced by the method of this aspect.

Detailed Description Text (2):
Sterilizing the inside of lumened devices has always posed a challenge to sterilization systems. Achieving rapid sterilization of lumened devices or other diffusion restricted articles at low temperatures and low concentrations of sterilant represents an even greater challenge. In the present invention, the shortcomings of the prior art sterilization systems are overcome by pretreating articles to be sterilized with an aqueous solution of hydrogen peroxide (i.e. a solution comprising both water and hydrogen peroxide) prior to exposure to a vacuum, or optionally, plasma. The method of the present invention provides for the rapid sterilization of lumened and non-lumened articles under conditions that will not damage the articles nor leave toxic residues on the sterile articles.

Detailed Description Text (3):
In the method of the present invention, dilute, aqueous solutions of hydrogen peroxide are delivered into direct contact with the article to be sterilized. In the case of a lumened device, the solution is delivered directly into the lumen. In the case of an

article having an area where diffusion of vapor is restricted, the solution is delivered to the interior of the diffusion restricted area. The hydrogen peroxide solution is delivered into the lumen or into contact with the article to be sterilized through means such as direct delivery, a static soaking process, a liquid flow-through process, or by aerosol spray. The aqueous solutions of hydrogen peroxide can be relatively dilute, e.g., as low as 1-3% or lower by weight, since sterilization is not achieved through contact with the hydrogen peroxide solution, but rather, is achieved at low temperatures and in short periods of time upon exposure to hydrogen peroxide vapor under vacuum or vacuum combined with plasma. The method of the present invention is particularly effective with articles having inaccessible or hard-to-reach places. Such articles include long, narrow lumens, hinges, and other articles having spaces where diffusion of vapors is restricted.

Detailed Description Text (5):
1. The lumen to be sterilized is exposed to an aqueous solution of dilute hydrogen peroxide. The aqueous solution can be delivered as a small amount directly into the lumen, or by static soaking, liquid flow-through, or aerosol spray.

Detailed Description Text (13):
To determine the efficacy of the sterilization method of the present invention, preliminary tests were first performed to evaluate the effect of dilute hydrogen peroxide solutions on contaminated surfaces in an open, non-diffusion restricted environment. These tests are described below in Example 1.

Detailed Description Text (15):
To evaluate the sterilization efficacy of dilute hydrogen peroxide solution alone, a biological challenge consisting of 2.5.times.10.sup.6 Bacillus stearothermophilus spores on a stainless steel scalpel blade was used. Inoculated blades were submerged in 40 ml of hydrogen peroxide solution in a 100 ml beaker. Four different concentrations of hydrogen peroxide solution were used: 3%, 6%, 9% and 12% by weight. The blades were allowed to soak in the peroxide solutions for various time periods. The blades were then removed from the solution and tested for sterility. The results of this testing are listed in Table 1 as a ratio of the number of inoculated blades which remain contaminated after treatment over the number of inoculated blades tested.

Detailed Description Text (16):
Complete sterilization was not effected until after the blades had been soaked in 12% hydrogen peroxide solution for at least 90 minutes. Moreover, none of the blades tested were sterilized after 2 hours in 6% hydrogen peroxide solution. It is clear from these data that contact with dilute hydrogen peroxide solution alone is ineffective at providing sterilization, unless extended soak times and concentrated solutions are used.

Detailed Description Text (17):
Testing was next performed to evaluate the effect on the sterilization of long, narrow lumens of a pretreatment step in which the lumens to be sterilized are exposed to hydrogen peroxide solution prior to exposure to a vacuum. The testing evaluated the efficacy of hydrogen peroxide vapor sterilization inside the lumens.

Detailed Description Text (20):
A biological challenge consisting of 1.9.times.10.sup.6 B. stearothermophilus spores on a stainless steel scalpel blade was used. Some inoculated blades were pretreated with a solution of aqueous hydrogen peroxide. Other inoculated blades, designated control blades, did not receive pretreatment with hydrogen peroxide. The pretreatment consisted of 5 minutes of static soaking in peroxide solution. The pretreated blades were blotted dry, and each blade was then placed inside a stainless steel lumen, 3 mm internal diameter (ID).times.50 cm length. The lumen had a center piece of 1.3 cm ID and 5 cm length. The pretreated blade was placed inside this center piece, and additional hydrogen peroxide solution was added into the center piece in various amounts. Control blades were handled identically, except that they did not receive pretreatment with hydrogen peroxide solution. The lumens were placed in a vacuum chamber, and the chamber was evacuated to 1 Torr and held there for 15 minutes, during which time the temperature increased from approximately 23.degree. C. to approximately 28.degree. C. Following exposure to the vacuum, the chamber was vented and the blades were removed from the chamber and tested for sterility. The results were as follows:

Detailed Description Text (24):
A biological challenge consisting of 1.9.times.10.sup.6 B. stearothermophilus spores on a stainless steel scalpel blade was used. Test A in Table 3 below consisted of the

inoculated blades being pretreated with a solution of 3% aqueous hydrogen peroxide. The pretreatment consisted of 5 minutes of static soaking in the peroxide solution. The pretreated blades were blotted dry, then placed into the center piece of a stainless steel lumen which varied in size, together with 10 .mu.l of 3% hydrogen peroxide solution. The center piece was 1.3 cm ID and 5 cm length. Test B in Table 3 below consisted of identically inoculated control blades which did not receive pretreatment with hydrogen peroxide. Each inoculated control blade was placed directly into the center piece of a stainless steel lumen together with 10 .mu.l of 3% hydrogen peroxide solution. The center piece had dimensions identical to those in Test A. Lumens of various dimensions were used to evaluate the effect on sterilization of lumen internal diameter and length. The lumens were placed in a vacuum chamber, and the chamber was evacuated to 1 Torr for 15 minutes. During this 15 minutes of the sterilization cycle, the temperature increased from approximately 23.degree. C. to approximately 28.degree. C. Following exposure to the vacuum, the chamber was vented and the blades were removed from the chamber and tested for sterility. The results are reported in Table 3, where "L/D Ratio" indicates the ratio of length to internal diameter.

Detailed Description Text (25):
All lumens having a L/D ratio greater than 50 which were tested under the conditions of Test A of Example 3 were sufficiently diffusion-restricted to be sterilized in this system. Thus, it is believed that other lumens having an L/D ratio greater than 50 should also provide a sufficient level of diffusion-restriction for sterilization in accordance with the present invention. This testing shows that, in direct contrast to prior art methods, sterility through diffusion of hydrogen peroxide vapor from inside the article to outside the article is easier to achieve in longer, narrower lumens than in shorter, wider lumens. This is believed to be due to the larger lumens allowing too much of the hydrogen peroxide vapor to diffuse out of the inside of the lumen during the sterilization process. Thus, the vapor does not contact the internal surfaces for a period of time sufficient or at a concentration sufficient to effect sterilization.

Detailed Description Text (26):
As discussed above, prior art methods of hydrogen peroxide vapor sterilization of lumens are generally limited to use on relatively short and wide lumens. In contrast to these prior art methods, the method of the present invention is effective on the interior of long, narrow lumens, including those longer than 27 cm in length and/or having an internal diameter of less than 3 mm.

Detailed Description Text (27):
To determine whether the ability of the sterilant vapor to diffuse within the system is a critical factor in achieving sterility, additional testing was performed to compare diffusion restricted and open, non-diffusion restricted systems. A non-diffusion restricted system is one in which the diffusion of vapors in and around the article is not restricted by narrow openings, long, narrow lumens, or the like. As used herein, "diffusion-restricted" refers to any one or more of the following properties: (1) the ability of an article placed within the sterilization system of the present invention to retain 0.17 mg/L or more hydrogen peroxide solution after one hour at 40.degree. C. and 10 torr; (2) having the same or more diffusion restriction than provided by a single entry/exit port of 9 mm or less in internal diameter and 1 cm or greater in length; (3) having the same or more diffusion restriction than provided by a lumen 27 cm in length and having an internal diameter of 3 mm; (4) having the same or more diffusion restriction than provided by a lumen having a ratio of length to internal diameter greater than 50; (5) the ability of an article placed within the sterilization system of the present invention to retain 17% or more of the hydrogen peroxide solution placed therein after one hour at 40.degree. C. and 10 torr; or (6) being sufficiently diffusion-restricted to completely sterilize a stainless steel blade within a 2.2 cm by 60 cm glass tube having a rubber stopper with a 1 mm by 50 cm stainless steel exit tube therein at a vacuum of 10 torr for one hour at 40.degree. C. in accordance with the present invention. It is acknowledged that characteristics (1) and (5) will vary depending on the initial concentration of hydrogen peroxide placed into the article; however, this can be readily determined by one having ordinary skill in the art.

Detailed Description Text (28):
As discussed in the Background of the Invention, articles having diffusion restricted areas are difficult to sterilize using known methods of hydrogen peroxide vapor sterilization, since these methods are dependent upon the diffusion of peroxide vapors from outside the article to the interior of the article. Testing performed to evaluate the importance of sterilant vapor diffusion is described in Example 4.

Detailed Description Text (30):

Hydrogen peroxide vapor sterilization was tested in both open and diffusion restricted systems. The open system consisted of stainless steel lumens having internal diameters of 1, 3, and 6 mm, and lengths of 15, 27, 40 and 50 cm. Stainless steel scalpel blades were inoculated with 1.9.times.10.sup.6 B. stearothermophilus spores, and the blades placed in the center piece of the lumen together with 10 .mu.l of 3% hydrogen peroxide solution. The dimensions of the center piece were 1.3 cm ID, 5 cm length and 6.6 cc volume.

Detailed Description Text (31):
The diffusion restricted system is illustrated in FIG. 1. Identically inoculated scalpel blades 5 were placed within the center pieces 10 of lumens 15 having dimensions identical to those described above. Ten .mu.l of 3% hydrogen peroxide solution was also added to the center piece 10 of the lumen 15. The lumen 15 was then placed within a 2.2 cm.times.60 cm glass tube 20. The tube 20 was closed at one end, and the open end was plugged with a rubber stopper 25 having a 1 mm.times.10 cm stainless steel tube 30 inserted through the stopper 25. Thus, gases entering or exiting the glass tube 20 could pass only through this 1 mm.times.10 cm opening.

Detailed Description Text (33):
Under the test conditions of Example 4, sterilization was not achieved in the shorter, wider lumens in the open system without pre-treatment with hydrogen peroxide. Pre-treatment, and other test conditions, such as higher peroxide concentration or longer treatment time, would likely allow sterilization of the 27 cm.times.3 mm lumen, which has an L/D ratio greater than 50. In the diffusion restricted system, the blades were sterilized in all sizes of lumens, using a 3% hydrogen peroxide solution.

Detailed Description Text (34):
These results indicate that providing a source of hydrogen peroxide within a diffusion restricted environment allows for complete sterilization within the system. It is the restriction of vapor diffusion in the system, not the length or internal diameter of the lumen per se that determines the efficacy of the hydrogen peroxide vapor sterilization. Again, however, these data show that, unlike the prior art methods of hydrogen peroxide vapor sterilization of lumens, the method of the present invention is effective even on non-diffusion-restricted articles when placed into a diffusion-restricted environment.

Detailed Description Text (37):
A stainless steel scalpel blade 5 was placed within a 2.2 cm.times.60 cm glass tube 20 which was closed at one end, as illustrated in FIG. 2. Each blade 5 had been inoculated with 1.9.times.10.sup.6 B. stearothermophilus spores. For some of the testing, the glass tube 20 was left open at one end, providing an open system. To create a diffusion restricted environment, the open end of the glass tube 20 was sealed with a rubber stopper 25 having a 1 mm.times.10 cm stainless steel tube 30 through its center. In both the open and diffusion restricted systems, hydrogen peroxide solution at a concentration of either 3% or 6% was added to the glass tube 20 in amounts of 50, 100, 150 or 200 .mu.l, together with the inoculated blade 5. The tube 20 was placed in a vacuum chamber, and the chamber evacuated to 1 Torr for 15 minutes, during which time the temperature increased from approximately 23.degree. C. to approximately 28.degree. C. The diffusion restricted system only was also tested at 1 Torr for 30 minutes, during which time the temperature increased from approximately 23.degree. C. to approximately 33.degree. C. The vacuum chamber was then vented, and the blades 5 removed from the tube 20 and tested for sterility. The results are listed in Table 5 below.

Detailed Description Text (38):
These results show that the addition of hydrogen peroxide solution, followed by exposure to vacuum, is ineffective for achieving rapid sterilization in an open system. Identical treatment in a diffusion restricted system, by comparison, results in complete sterilization, except at the very weakest concentration of hydrogen peroxide solution in an amount of only 50 .mu.l. Sterilization can be effected, however, by increasing the exposure to the vacuum.

Detailed Description Text (39):
Thus, the method of the present invention, wherein small amounts of hydrogen peroxide solution are delivered to the article to be sterilized prior to exposure to a vacuum, is an effective method of sterilization. The method does not depend on the diffusion of sterilant vapor into the article being sterilized. Rather, the hydrogen peroxide vapor is created by the vacuum within the system. This vapor is prevented from leaving the system too quickly, because the diffusion of the sterilant vapor from the inside of the

article to the outside of the article is slowed. In a diffusion restricted environment, the vapor therefore contacts the article to be sterilized for a period of time sufficient to effect complete sterilization. In addition, unlike the prior art methods where the water in the peroxide solution is vaporized first and becomes a barrier to the penetration of the peroxide vapor, the method of the present invention removes the water from the system first, thereby concentrating the hydrogen peroxide vapor remaining in the system. More importantly, in the present invention, the diffusion of vapor is from the inside to outside rather than outside to inside as in the prior art. As a result, diffusion-restriction in the present invention serves to increase the effectiveness of sterilization rather than to decrease the effectiveness, as in the prior art.

Detailed Description Text (42):
A stainless steel scalpel blade 5 was placed within a 2.2 cm.times.60 cm glass tube 20 which was closed at one end, as shown in FIG. 2. Each blade 5 had been inoculated with 1.9.times.10.sup.6 B. stearothermophilus spores. To create a diffusion restricted environment, the open end of the glass tube 20 was sealed with a rubber stopper 25 having a 1 mm.times.10 cm stainless steel tube 30 through its center. Hydrogen peroxide solution at a concentration of 3% was added to the glass tube 20 in amounts of 50, 100, 150 or 200 .mu.l, together with the inoculated blade 5. The tube 20 was placed in a vacuum chamber, and subjected to various pressures for 15 minutes, during which time the temperature increased from approximately 23.degree. C. to approximately 28.degree. C. In a further experiment to determine the effect of increased temperature on the system, the tube 20 was first heated to 45.degree. C., then subjected to 50 Torr pressure for 15 minutes. The results were as follows.

Detailed Description Text (43):
These data show that sterilization can be achieved in diffusion restricted environments at pressures up to about 25 Torr at 28.degree. C. At pressures of 30 Torr and higher, sterilization was not achieved; this is believed to be due to the fact that the vapor pressure of hydrogen peroxide at 28.degree. C. is approximately 28 Torr. Thus, at higher pressures, the liquid hydrogen peroxide inside the glass tube was not vaporizing. This was confirmed by the testing done at 50 Torr pressure at 45.degree. C., wherein sterilization was achieved. The vapor pressure of hydrogen peroxide is increased at 45.degree. C., thus, the hydrogen peroxide was vaporized at 50 Torr, effectively sterilizing the blade placed inside the tube.

Detailed Description Text (44):
Accordingly, in order to achieve sterilization using the method of the present invention, the temperature and pressure within the vacuum chamber should be such that vaporization of the aqueous hydrogen peroxide solution is achieved, i.e. the system should preferably be operated below the vapor pressure of the hydrogen peroxide. The pressure needs to be below the vapor pressure of hydrogen peroxide, such that the hydrogen peroxide solution present in the system is vaporized and diffuses from the interior of the diffusion restricted environment to the outside. Alternatively, the hydrogen peroxide can be vaporized locally where the system remains above the vapor pressure by introducing energy to the site of the peroxide, such as through microwaves, radio waves, or other energy sources.

Detailed Description Text (47):
A stainless steel scalpel blade 5 was placed within a 2.2 cm.times.60 cm glass tube 20 which was closed at one end, as illustrated in FIG. 2. Each blade 5 had been inoculated with 1.9.times.10.sup.6 B. stearothermophilus spores. To create a diffusion restricted environment, the open end of the glass tube 20 was sealed with a rubber stopper 25 having a 1 mm.times.10 cm stainless steel tube 30 through its center. Hydrogen peroxide solution at a concentration of 3% was added to the glass tube 20 in amounts of 50, 100, 150 or 200 .mu.l together with the inoculated blade 5. The tube 20 was placed in a vacuum chamber, and the chamber evacuated to 5 Torr. To vary the pressure within the chamber, the valve to the vacuum pump was closed, such that the pressure within the chamber rose from 5 Torr to 6.15 Torr after 15 minutes, during which time the temperature increased from approximately 23.degree. C. to approximately 28.degree. C. In a second test, the tube 20 was placed in the chamber and the chamber was evacuated to 50 Torr. The temperature of the glass tube 20 was increased to 45.degree. C. after the evacuation of the chamber was complete. The tube 20 was treated for 15 minutes. The results of these tests are reported below.

Detailed Description Text (48):
These results show that maintaining a constant pressure or temperature is not required in the diffusion restricted environment to effect sterilization. Under the conditions

tested, the hydrogen peroxide is vaporized and kept in contact with the device to be sterilized for a time sufficient to effect complete sterilization.

Detailed Description Text (49):
The method of the present invention relies on the delivery of liquid hydrogen peroxide to the article to be sterilized prior to vacuum or plasma treatment. The following testing was performed to determine the effect of the location of the delivery of the hydrogen peroxide within the diffusion restricted environment.

Detailed Description Text (51):
A stainless steel scalpel blade 5 was inoculated with 1.9.times.10.sup.6 B. stearothermophilus spores, and the blade 5 placed in the center piece 10 of a lumen 15 as illustrated in FIG. 1. The dimensions of the center piece 10 were 1.3 cm ID, 5 cm length and 6.6 cc volume, while the lumen itself varied in size, having an ID of 1, 3 or 6 mm, and a length of 15, 27, 40 or 50 cm. The lumen 15 was placed within a 2.2 cm.times.60 cm glass tube 20. The tube 20 was closed at one end, and the open end was plugged with a rubber stopper 25 having a 1 mm.times.10 cm stainless steel tube 30 placed through the stopper 25. Thus, gases entering or exiting the glass tube 20 could pass only through this 1 mm.times.10 cm opening. 10 .mu.l of 3% hydrogen peroxide solution was placed inside the lumen 15, or 100 .mu.l of 3% hydrogen peroxide solution was placed inside the glass tube 20, but outside the stainless steel lumen 15. The glass tube 20 was then placed in a vacuum chamber, which was sealed and evacuated to 1 Torr for 15 minutes, during which time the temperature increased from approximately 23.degree. C. to approximately 28.degree. C. Results of this testing are as follows.

Detailed Description Text (52):
These data show that, under the test conditions of Example 8, sterilization did not occur within the inner lumen when the hydrogen peroxide solution was placed outside the lumen in a diffusion restricted environment, but that complete sterilization was effected when the hydrogen peroxide solution was placed inside all of the lumens in a diffusion restricted environment. When the hydrogen peroxide vapor must diffuse from outside to inside, the sterilant vapor cannot enter the inner lumen in a diffusion restricted environment unless the lumen is sufficiently large. Thus, when the hydrogen peroxide solution was placed outside the lumen, only the shortest, widest lumens allowed sufficient vapor penetration to allow sterilization inside the lumen. These data confirm that prior art methods which require diffusion of sterilant vapor from outside the article to the interior article cannot achieve sterilization in diffusion restricted environments under these conditions. In contrast, under the same conditions except where the hydrogen peroxide was placed inside the article, allowing hydrogen peroxide to diffuse from inside to outside, complete sterilization occurred with much lower amounts of hydrogen peroxide.

Detailed Description Text (55):
A stainless steel scalpel blade 5 was inoculated with 1.9.times.10.sup.6 B. stearothermophilus spores, and placed in a 2.2 cm.times.60 cm glass tube 20 as illustrated in FIG. 2. The tube 20 was closed at one end, and the open end was plugged with a rubber stopper 25. Stainless steel tubing 30 of various dimensions was inserted through the stopper 25. Thus, gases entering or exiting the glass tube 20 could pass only through the opening in the tubing 30, which varied from 1 mm to 6 mm in diameter. Three percent hydrogen peroxide solution in volumes ranging from 50 .mu.L to 200 .mu.L was also placed inside the glass tube 20. The glass tube 20 was then placed in a vacuum chamber, which was sealed and evacuated to 5 Torr for 15 minutes, during which time the temperature increased from approximately 23.degree. C. to approximately 28.degree. C. In addition, three lumens were tested at 10 Torr for 15 minutes with 3% hydrogen peroxide. The results of this testing are listed below in Table 9.

Detailed Description Text (56):
Complete sterilization was achieved in the majority of the environments tested. Sterilization could not be achieved at 5 torr using the shortest length of stainless steel tubing and only 50 .mu.l hydrogen peroxide solution. Greater volumes of hydrogen peroxide must be used in these systems.

Detailed Description Text (57):
These data also confirm that the vacuum pressure affects sterilization efficacy, since the container with the shortest and widest exit tube could provide sterilization at 10 Torr, but not at 5 Torr. At too low pressures (such as pressures below 5 Torr in the conditions tested) however, it appears that the hydrogen peroxide vapor is pulled from the interior of the article being sterilized too quickly, resulting in an insufficient amount of hydrogen peroxide vapor being allowed to contact the interior of the device

to effect sterilization. It would appear that although a pressure of 5 torr produces acceptable results, a pressure of approximately 10 Torr is better under the conditions tested.

Detailed Description Text (60):
For this testing, a diffusion restricted system was tested. 1.2.times.10.sup.6 B. stearothermophilus spores were inoculated onto non-woven polypropylene pieces. As illustrated in FIG. 1, the inoculated pieces 5 were placed inside the center piece 10 of a plastic lumen 15, together with 10 .mu.l of 3% hydrogen peroxide solution. The center piece 10 was made of Teflon.TM. and had dimensions of 1.3 cm.times.5 cm. The lumen 15 varied from 1 mm to 6 mm ID, and 15 cm to 50 cm in length. Teflon.TM. was used for the 1 mm lumen, polyethylene was used for the 3 mm and 6 mm lumen. The lumen 15 was then placed within a 2.2 cm.times.60 cm glass tube 20. The glass tube 20 was closed on one end, and the open end was sealed with a rubber stopper 25 having a 1 mm.times.10 cm piece of PTFE tubing 30 through it. The glass tube 20 was placed in the vacuum chamber and treated for 15 minutes at 1 Torr, during which time the temperature increased from approximately 23.degree. C. to approximately 28.degree. C. The results of this testing are set forth below.

Detailed Description Text (62):
To further confirm this, 2.1.times.10.sup.6 B. stearothermophilus spores were inoculated on stainless steel blades, and 1.2.times.10.sup.6 B. stearothermophilus spores were inoculated onto non-woven polypropylene pieces. As shown in FIG. 2, the blades 5 or non-woven polypropylene pieces 5 were placed inside a 2.2 cm.times.60 cm glass tube 20 together with 50 .mu.l of 3% hydrogen peroxide solution. One end of the tube was closed, and the open end was sealed with a rubber stopper 25 having either a 1 mm.times.10 cm stainless steel tube 30 therein, or a 1 mm.times.10 cm piece of Teflon.TM. tubing 30 therein. The glass tube 20 was placed inside a vacuum chamber and treated for 15 minutes at 5 Torr, during which time the temperature increased from approximately 23.degree. C. to approximately 28.degree. C. The results are as follows.

Detailed Description Text (63):
Thus, all four combinations of metal and plastic provide for effective hydrogen peroxide vapor sterilization in a diffusion restricted environment. This testing confirms that the method of the present invention is an effective sterilization method for diffusion restricted articles, and can be used on a wide variety of such articles, regardless of the materials used to form them.

Detailed Description Text (66):
Stainless steel blades were inoculated with 2.1.times.10.sup.6 B. stearothermophilus spores. The blades 5 were placed inside a 2.2 cm.times.60 cm glass tube 20 as illustrated in FIG. 2, along with various amounts of 3% hydrogen peroxide solution. The glass tube 20 was placed in a vacuum chamber and subjected to different pressures and different temperatures for various periods of time. During the sterilization cycles reported in Table 11A, the temperature increased from approximately 23.degree. C. to the temperatures indicated. In the experiments reported in Table 11B, the chamber was heated to approximately 45.degree. C. In an alternative embodiment, rather than heating the chamber, the temperature of the peroxide solution itself can be heated. In the experiments reported in Table 11C, the temperature increased from approximately 23.degree. C. to approximately 28.degree. C. during the minute period of exposure to vacuum.

Detailed Description Text (67):
Under the test conditions of Example 11, large volumes of hydrogen peroxide solution were ineffective at achieving sterilization when vacuum was applied for only very short periods of time. This is believed to be at least partially because water vaporizes more quickly than hydrogen peroxide. Thus, the water present in the aqueous solution will vaporize first, and more time is needed to vaporize the hydrogen peroxide. This also explains why the larger volumes of hydrogen peroxide solution were effective at achieving sterilization at higher temperatures; the vaporization of the hydrogen peroxide occurs sooner at higher temperatures. Thus, when more water is present in the system, either higher temperatures or more time is required to achieve sterilization.

Detailed Description Text (68):
Again, it would appear from these data that slightly higher pressures, i.e. 10 Torr, achieve more effective sterilization under these conditions. This is believed to be because at higher pressures, more hydrogen peroxide vapor is retained inside the system. At too low a pressure, the hydrogen peroxide vapor is pulled out of the system too quickly.

Detailed Description Text (71):
Various concentrations of peroxide were used in a system substantially as described in connection with FIG. 2. In this system, the exit tube 35 was a stainless steel tube having a length of 50 cm and an internal diameter of 1 mm. A stainless steel blade inoculated with 1.9.times.10.sup.6 spores of B. stearothermophilus was placed within the container which was a 2.2 cm.times.60 cm glass tube. Various amounts of 3% hydrogen peroxide were introduced into the container. The container was placed in a vacuum chamber of 173 liters, and the pressure reduced to 10 Torr for a period of one hour, during which time the temperature increased from approximately 23.degree. C. to approximately 40.degree. C. Sporicidal activity was evaluated at each concentration of peroxide. In addition, the amount of peroxide remaining in the container after the sterilization process was evaluated by standard titration techniques, whereby the peroxide was reacted with potassium iodide and titrated with sodium thiosulfate. Results are shown in Table 12 where "N/D" indicates not determined.

Detailed Description Text (72):
The results reported in Table 12 indicate that 1.0 mg/L of 3% liquid peroxide were required in the system tested to effect sterilization. Further, under the conditions tested, a concentration of 0.17 mg/L of peroxide remaining in the system was sufficient to provide complete sterilization. These data also show that the glass tube used in these experiments provided a sufficient level of diffusion restriction to retain 17% of the hydrogen peroxide placed therein.

Detailed Description Text (79):
A stainless steel blade was inoculated with 2.1.times.10.sup.6 B. stearothermophilus spores. The blade 5 was placed inside a 2.2 cm.times.60 cm glass tube 20 as shown in FIG. 3, together with various amounts of 3% hydrogen peroxide solution. One end of the tube was closed, and the open end was sealed with a rubber stopper 25 having a syringe filter 35 inserted therein. The glass tube 20 was placed inside a vacuum chamber and treated for 15 minutes at 5 Torr, during which time the temperature increased from approximately 23.degree. C. to approximately 28.degree. C. As a control, identically inoculated blades were placed inside 2.2 cm.times.60 cm glass tubes. The open end of the tubes was left open, no stopper or syringe filter was used. Thus, the diffusion of vapor from the interior of the tube was not restricted.

Detailed Description Text (81):
As is apparent from these results, certain brands of filters do not create a sufficiently diffusion restricted environment at 5 Torr pressure when only 50 .mu.L of hydrogen peroxide solution is placed in the system. Other brands of filters did provide sufficient diffusion restriction; these brands of filters had either longer lumens or smaller filter pore size. Using larger volumes of peroxide solution, 10 Torr pressure, or serial filters enhances the efficacy of the sterilization system. This is important, as filters, including ones made of Tyvek.TM., are often used in packaging of sterile articles to prevent re-contamination with bacteria. These filters generally have a pore size of 1 .mu.m or less, or in the case of Tyvek.TM., create a tortuous path which bacteria cannot cross. In the present invention, filters can be used in combination with other packaging means to create a diffusion restricted environment to effect sterilization, and the sterile article can remain inside the packaging during storage prior to use; the filter will prevent re-contamination of the sterile article.

Detailed Description Text (85):
These results show that peracetic acid, in which hydrogen peroxide coexists, can also be used in the sterilization method of the present invention.

Detailed Description Text (86):
It was discovered that by delivering small amounts of hydrogen peroxide solution to an article to be sterilized prior to exposure to vacuum, sterilization could be effected at lower temperatures and in short periods of time. The following testing was performed to evaluate different methods of delivering hydrogen peroxide solution to the article to be sterilized. Further, the efficacy of vacuum treatment and plasma treatment following pretreatment with aqueous hydrogen peroxide were compared. The testing is described in Example 16 below.

Detailed Description Text (88):
In a first series of tests, stainless steel blades were inoculated with 2.5.times.10.sup.6 B. stearothermophilus spores. The blades were placed in the expanded center piece of a 3 mm.times.50 cm stainless steel lumen. The lumen was placed in a 1000 ml beaker containing 800 ml of hydrogen peroxide solution. The lumen was soaked

for 5 minutes in 3% hydrogen peroxide solution. The number of surviving organisms following this initial soak was determined. The lumens were removed from the hydrogen peroxide solution and the outside blotted dry with paper towels. The inside of the lumens were dried by placing one end of the lumen into a flask and blowing with a three second burst of compressed air. The lumens were shaken, and the blowing and shaking repeated until no more solution was blown out. Subsequently, the lumen was placed in a sterilization chamber and exposed to either a vacuum of 0.5 Torr for 15 minutes, or plasma for 15 minutes at 0.5 Torr. After 15 minutes of vacuum, the temperature increased from approximately 23.degree. C. to approximately 28.degree. C. The results are set forth below in Table 16A.

Detailed Description Text (89):
A five minute soak in 3% hydrogen peroxide solution was an effective means for delivering the hydrogen peroxide into the lumen prior to vacuum or plasma treatment. As noted before, treatment with hydrogen peroxide solution only is ineffective to achieve sterilization using dilute solutions and short soak times. Delivery of hydrogen peroxide solution via static soaking is at least as effective a way to deliver the hydrogen peroxide as depositing small volumes directly into the lumen of the device.

Detailed Description Text (90):
Flow-through delivery of hydrogen peroxide was tested next. Here, stainless steel blades were inoculated with 2.5.times.10.sup.6 B. stearothermophilus spores. The blades were placed in the expanded center piece of a 3 mm.times.50 cm stainless steel lumen. Hydrogen peroxide solution at 3% concentration was delivered to the lumen at a flow rate of 0.1 L/min, using a peristaltic pump. The lumen was dried as described above. Following pretreatment with hydrogen peroxide solution, the lumen was then placed in a sterilization chamber and exposed to either a vacuum of 0.5 Torr for 15 minutes, or plasma for 15 minutes at 0.5 Torr. The results are set forth below in Table 16B.

Detailed Description Text (91):
Delivery of the hydrogen peroxide solution via constant flow is also an effective way to deliver hydrogen peroxide to the system.

Detailed Description Text (92):
Finally, the effect of delivery of hydrogen peroxide by aerosol spray was tested. Stainless steel blades were inoculated with 2.5.times.10.sup.6 B. stearothermophilus spores. The inoculated blades were placed in the expanded center piece of a 3 mm.times.50 cm stainless steel lumen. Three percent hydrogen peroxide solution was delivered to the lumen via a 3 second aerosol spray. Aerosol spray rate was determined to be 0.04 L/min. After a 5 minute wait following pretreatment with hydrogen peroxide, the lumen was dried as described above and the lumen was then placed in a sterilization chamber and exposed to either a vacuum of 0.5 Torr for 15 minutes, or plasma for 15 minutes at 0.5 Torr. The results are set forth below in Table 16C.

Detailed Description Text (93):
Flow-through of hydrogen peroxide as either a liquid solution or aerosol can also be achieved by introducing increased pressure at the delivery end or decreased pressure at the exit end of the device to be treated.

Detailed Description Text (94):
It is evident from the data in Tables 16A-16C that all three methods of delivering hydrogen peroxide solution to the article to be sterilized provided for effective sterilization. Thus, it appears that a number of different methods of delivery can be used, as long as the hydrogen peroxide solution is present in the system prior to exposure to vacuum or plasma.

Detailed Description Text (95):
Finally, the efficacy of pretreatment with hydrogen peroxide prior to a sterilization cycle which combines exposure to hydrogen peroxide vapor, vacuum, and plasma was evaluated. The testing was as follows.

Detailed Description Text (97):
Stainless steel blades were inoculated with 2.5.times.10.sup.6 B. stearothermophilus spores. The blades were soaked in 3% hydrogen peroxide solution for either 1 or 5 minutes. The blades were then placed in the expanded center piece of a 3 mm.times.50 cm stainless steel lumen. The lumen was then placed in a sterilization chamber which was evacuated to approximately 0.5 Torr. The sterilization cycle consisted of 15 minutes of hydrogen peroxide vapor diffusion with a minimum of 6 mg/L hydrogen peroxide, followed by 15 minutes of plasma at 400 watts. Following the plasma treatment, the chamber was

vented and the blades tested for sterility. The results are shown below.

Detailed Description Text (98):
Processing the lumens in a hydrogen peroxide vapor and plasma cycle alone left an average of 30 surviving organisms per blade. Pretreating the blades by soaking in 3% hydrogen peroxide solution for 5 minutes alone left an average of 8.2.times.10.sup.5 surviving organisms per blade. Thus, under the test conditions, a combination of hydrogen peroxide vapor exposure and plasma exposure, which has been found to be effective for many articles, was ineffective in a diffusion restricted environment. However, by pretreating the article to be sterilized with dilute hydrogen peroxide solution prior to exposure to hydrogen peroxide vapor and plasma, complete sterilization can be achieved.

Detailed Description Text (99):
While the invention has been described in connection with liquid sterilant solutions containing hydrogen peroxide, it will be appreciated by those having ordinary skill in the art that equivalent sterilization methods can be adapted for other sterilant liquids. In an alternative embodiment, a sterilant having a vapor pressure lower than that of water or other solvent in which the sterilant is provided is used. For such sterilants, it is only important that the vapor pressure be lower than that of the solvent within the temperature ranges contemplated herein. Such sterilants can be adapted for the techniques described herein with only minor adjustments made for the differences in vapor pressure between peroxide and such other sterilant, as can be readily determined by those having ordinary skill in the art. As long as the local vapor pressure at the site of the sterilant liquid is below the vapor pressure of the sterilant, sterilization can be achieved substantially as described hereinabove.

Detailed Description Text (101):
Achieving rapid sterilization of lumened devices at low temperatures using low concentrations of sterilants has, until now, been exceedingly challenging. A superior method of sterilization has been discovered which overcomes the problems of the known methods. By pretreating articles to be sterilized with an aqueous solution of hydrogen peroxide prior to exposure to a vacuum, rapid sterilization can be achieved at low temperatures, without damage to the articles, without leaving toxic residues behind, and without the need to attach special vessels. The method of the present invention is efficient, nonhazardous, and inexpensive as well.

Detailed Description Paragraph Table (2):
TABLE 2 Effect of Pretreatment and Hydrogen Peroxide Concentration on Sterilization of the Interior of Lumens Additional peroxide added into the Blades not pretreated Blades pretreated in center piece with peroxide peroxide solution (A) With 1% hydrogen peroxide solution and vacuum 10 .mu.L + + 20 .mu.L + + 30 .mu.L + + 40 .mu.L + + 50 .mu.L + + 100 .mu.L + . 150 .mu.L + . 200 .mu.L . . 250 .mu.L . . (B) With 3% hydrogen peroxide solution and vacuum 10 .mu.L . . 20 .mu.L . . 30 .mu.L . . 40 .mu.L . . 50 .mu.L . . 100 .mu.L . . 150 .mu.L . . 200 .mu.L . . 250 .mu.L . . (C) With 6% hydrogen peroxide solution and vacuum 10 .mu.L . . 20 .mu.L . . 30 .mu.L . . 40 .mu.L . . 50 .mu.L . .

Detailed Description Paragraph Table (4):
TABLE 4 Hydrogen Peroxide Vapor Sterilization in Open and Diffusion Restricted Systems Peroxide System amount Length 1 mm ID 3 mm ID 6 mm ID Open 10 .mu.L of 3% 50 cm - - - 40 cm - - - 27 cm - + + 15 cm - + + Diffusion 10 .mu.L of 3% 50 cm - - - Restricted 40 cm -.- - Environment 27 cm - - - 15 cm - - -

Detailed Description Paragraph Table (5):
TABLE 5 Hydrogen Peroxide Vapor Sterilization in Open and Diffusion Restricted Systems 50 .mu.L 100 .mu.L 150 .mu.L 200 .mu.L Open System, 15 minutes vacuum at 1 Torr: 3% peroxide + + + + 6% peroxide + + + + Diffusion Restricted System, 15 minutes vacuum at 1 Torr: 3% peroxide + - - - 6% peroxide - - - - Diffusion Restricted System, 30 minutes vacuum at 1 Torr: 3% peroxide - - - -

Detailed Description Paragraph Table (6):
TABLE 6 Effect of Temperature and Pressure on a Diffusion Restricted System 50 .mu.L 100 .mu.L 150 .mu.L 200 .mu.L 15 minutes vacuum with 3% hydrogen peroxide solution: 1 torr pressure + - - - 5 torr pressure - - - - 10 torr pressure - - - - 15

torr pressure - - - - 20 torr pressure - - - - 25 torr pressure - - - - 30 torr pressure + + + + 35 torr pressure + + + + 40 torr pressure + + + + 45 torr pressure + + + + 50 torr pressure + + + + 15 minutes vacuum with 3% hydrogen peroxide at 45.degree. C.: 50 torr pressure - - - -

Detailed Description Paragraph Table (8):

TABLE 8 Effect of Hydrogen Peroxide Solution Placed Outside Inner Lumen Peroxide amount Length 1 mm ID 3 mm ID 6 mm ID 10 .mu.L of 3% 50 cm - - - in lumen 40 cm - - - 27 cm - - - 15 cm - - - 50 cm + + + 100 .mu.L of 3% 40 cm + + + in glass tube 27 cm + + + 15 cm + + -

Detailed Description Paragraph Table (9):

TABLE 9 Effects of Tubing Dimension and Vacuum Pressure on Sterilization SS tubing 50 .mu.L 100 .mu.L 150 .mu.L 200 .mu.L 15 minutes vacuum at 5 Torr with 3% hydrogen peroxide 1 mm .times. 10 cm - - - - 1 mm .times. 5 cm - - - - 1 mm .times. 2.5 cm + - - - 3 mm .times. 10 cm - - - - 3 mm .times. 5 cm - - - - 3 mm .times. 2.5 cm + - - - 6 mm .times. 10 cm - - - - 6 mm .times. 5 cm + - - - 6 mm .times. 2.5 cm + - - - 15 minutes vacuum at 10 Torr with 3% hydrogen peroxide 1 mm .times. 2.5 cm - 3 mm .times. 2.5 cm - 6 mm .times. 2.5 cm -

Detailed Description Paragraph Table (17):

TABLE 14 Sporicidal Activity of H.sub.2 O.sub.2 Solution with Vacuum in a Container Having a Syringe Filter 15 minutes vacuum and 3% hydrogen peroxide: 50 .mu.L 100 .mu.L 150 .mu.L 200 .mu.L (a) Without syringe filter and stopper: 5 Torr + + + + 10 Torr + + + + (b) With MFS .TM. PTFE 25 mm syringe filter: (1) 0.2 .mu.m membrane filter 5 Torr + - - - 10 Torr - - - - (2) 0.5 .mu.m membrane filter 5 Torr + - - - 10 Torr - - - - (3) With 2 MFS .TM. filters together at 5 Torr pressure Two 0.2 .mu.m filters - Two 0.5 .mu.m filters - (c) With Nalgene .TM. PTFF 50 mm syringe filter: (1) 0.2 .mu.m membrane filter 5 Torr - - - - 10 Torr - - - - (2) 0.45 .mu.m membrane filter 5 Torr - - - - 10 Torr - - - - (d) With Whatman Anotop .TM. 10 Plus syringe filter: (1) 0.02 .mu.m membrane filter 5 Torr - - 10 Torr - - (2) 0.1 .mu.m membrane filter 5 Torr - - 10 Torr - - (e) With Gelman Acrodisc .TM. CR PTFE syringe filter: (1) 0.2 .mu.m membrane filter 5 Torr + - 10 Torr - - (2) 0.45 .mu.m membrane filter 5 Torr + - 10 Torr - - (3) 1.0 .mu.m membrane filter 5 Torr + - 10 Torr - -

Detailed Description Paragraph Table (22):

TABLE 17 Effects of H.sub.2 O.sub.2 Solution Soak on Sporicidal Activity in Stainless Steel Lumens Prior to a Hydrogen Peroxide Vapor and Plasma Cycle Sterility Test Results Conc. H.sub.2 O.sub.2 Soak Time Soak Alone Soak + Cycle 3% 1 min 4/4 0/4 5 min 4/4 0/4

CLAIMS:

1. A method for sterilizing an interior of a device having a lumen, comprising:

contacting the interior of said lumen with a liquid solution comprising hydrogen peroxide; and

exposing said device to a selected negative pressure and a selected temperature to vaporize said hydrogen peroxide,

wherein said lumen has a length and diameter which provide the same or more diffusion restriction than provided by a reference lumen 27 cm in length and having an internal diameter of 3 mm, at said selected pressure and said selected temperature,

and wherein said hydrogen peroxide vapor diffuses from inside to outside of said lumen, for a time period sufficient to effect sterilization of said lumen by hydrogen peroxide vapor.

9. The method of claim 1, wherein if the exposing step is conducted at 40.degree. C. and 10 torr for one hour and if in the contacting step 1 mg of hydrogen peroxide per liter of lumen volume is introduced into said lumen, said lumen is sufficiently diffusion restricted to retain a concentration of 0.17 mg or more hydrogen peroxide per liter of lumen volume, wherein 0.17 mg/L is the total concentration of hydrogen

peroxide liquid at 1 atmosphere pressure, remaining after the exposing step.

10. The method of claim 1, wherein if the exposing step is conducted at 40.degree. C. and 10 torr for one hour and if in the contacting step 1 mg of hydrogen peroxide per liter of lumen volume is introduced into said lumen, said lumen is sufficiently diffusion restricted to retain 17% or more of the total hydrogen peroxide introduced therein after the exposing step, wherein the 17% is the hydrogen peroxide liquid at 1 atmosphere pressure, remaining after the exposing step.

21. The method of claim 1, wherein said exposing step comprises exposing said device to pressure less than the vapor pressure of hydrogen peroxide.

24. A method for sterilizing an interior and an exterior of an article having a lumen, comprising:

contacting the interior of said lumen with a liquid solution comprising hydrogen peroxide; and

placing said article in a diffusion-restricted environment, said contacting and placing steps being performed in either order; followed by

exposing said diffusion-restricted environment to a selected negative pressure and a selected temperature to vaporize said hydrogen peroxide for a time period sufficient to effect sterilization of the interior and exterior of said article by hydrogen peroxide vapor, wherein said lumen has a length and diameter which provide the same or more diffusion restriction than provided by a reference lumen 27 cm in length and having an internal diameter of 3 mm, at said selected pressure and said selected temperature.

26. The method of claim 25, additionally comprising contacting the article with a liquid solution comprising hydrogen peroxide again after the placing step.

29. The method of claim 24, wherein if the exposing step is conducted at 40.degree. C. and 10 torr for one hour and if in the contacting step 1 mg of hydrogen peroxide per liter of lumen volume is introduced into said lumen, said diffusion restricted environment is sufficiently diffusion restricted to retain 17% or more of the total hydrogen peroxide placed therein after the exposing step, wherein the 17% is the hydrogen peroxide liquid at one atmosphere pressure, remaining after the exposing step.

30. The method of claim 24, wherein if the exposing step is conducted at 40.degree. C. and 10 torr for one hour and if in the contacting step 1 mg of hydrogen peroxide per liter of lumen volume is introduced into said lumen, said diffusion restricted environment is sufficiently diffusion restricted to retain a concentration of 0.17 mg or more hydrogen peroxide after the exposing step per liter of lumen volume wherein said 0.17 mg/L or more hydrogen peroxide is the total concentration of hydrogen peroxide liquid at one atmosphere pressure, remaining after the exposing step.

49. A method for sterilizing a device having a lumen, comprising:

contacting the interior of said lumen with a liquid solution comprising hydrogen peroxide; and

exposing said device to a selected negative pressure and a selected temperature to vaporize said hydrogen peroxide,

wherein said lumen has a length and a diameter which provide the same or more diffusion restriction than provided by a reference lumen having a length to internal diameter ratio of 50 at said selected pressure and said selected temperature,

and wherein said hydrogen peroxide vapor diffuses from inside to outside of said lumen, for a time period sufficient to effect sterilization of said lumen by hydrogen peroxide vapor.

66. The method of claim 49, wherein said exposing comprises exposing said device to pressure less than the vapor pressure of hydrogen peroxide.

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DOCUMENT-IDENTIFIER: US 5961921 A
TITLE: Method of sterilization in diffusion restricted environments

Brief Summary Text (6):
Sterilization using liquid hydrogen peroxide solution has been found to require high concentration of sterilant, extended exposure time and/or elevated temperatures. However, sterilization using hydrogen peroxide vapor has been shown to have some advantages over other chemical sterilization processes (see, e.g., U.S. Pat. Nos. 4,169,123 and 4,169,124). The combination of hydrogen peroxide with a plasma provides certain additional advantages, as disclosed in U.S. Pat. No. 4,643,876, issued Feb. 17, 1987 to Jacobs et al.. U.S. Pat. No. 4,756,882, issued Jul. 12, 1988 also to Jacobs et al. discloses the use of hydrogen peroxide vapor, generated from an aqueous solution of hydrogen peroxide, as a precursor of the reactive species generated by a plasma generator. The combination of hydrogen peroxide vapor diffusing into close proximity with the article to be sterilized and plasma acts to sterilize the articles, even within closed packages. Further, these methods of combining hydrogen peroxidevapor with a plasma, while useful in "open" systems, have been found to be inadequate to effect sterilization in articles having diffusion-restricted areas, since the methods are dependent upon diffusion of the sterilant vapor into close proximity with the article before sterilization can be achieved. Thus, these methods have been found to require high concentration of sterilant, extended exposure time and/or elevated temperatures when used on long, narrow lumens. For example, lumens longer than 27 cm and/or having an internal diameter of less than 0.3 cm have been particularly difficult to sterilize. Thus, no simple, safe, effective method of sterilizing smaller lumens exists in the prior art.

Brief Summary Text (7):
The sterilization of articles containing diffusion-restricted areas, such as long narrow lumens, therefore presents a special challenge. Methods that use hydrogen peroxide vapor that has been generated from an aqueous solution of hydrogen peroxide have certain disadvantages, because:

Brief Summary Text (8):
1. Water has a higher vapor pressure than hydrogen peroxide and will vaporize faster than hydrogen peroxide from an aqueous solution.

Brief Summary Text (9):
2. Water has a lower molecular weight than hydrogen peroxide and will diffuse faster than hydrogen peroxide in the vapor state.

Brief Summary Text (10):
Because of this, when an aqueous solution of hydrogen peroxide is vaporized in the area surrounding the items to be sterilized, the water reaches the items first and in higher concentration. The water vapor therefore becomes a barrier to the penetration of hydrogen peroxide vapor into diffusion restricted areas, such as small crevices and long narrow lumens. One cannot solve the problem by removing water from the aqueous solution and using more concentrated hydrogen peroxide, since, among other reasons, concentrated solutions of hydrogen peroxide greater than 65% by weight can be hazardous due to the oxidizing nature thereof.

Brief Summary Text (11):
U.S. Pat. No. 4,952,370 to Cummings et al. discloses a sterilization process wherein aqueous hydrogen peroxide vapor is first condensed on the article to be sterilized, and then a source of vacuum is applied to the sterilization chamber to evaporate the water and hydrogen peroxide from the article. This method is suitable to sterilize surfaces, however, it is ineffective at rapidly sterilizing diffusion-restricted areas, such as

those found in lumened devices, since it too depends on the diffusion of the hydrogen peroxide vapor into the lumen to effect sterilization.

Brief Summary Text (12):
U.S. Pat. No. 4,943,414, entitled "Method for Vapor Sterilization of Articles Having Lumens," and issued to Jacobs et al., discloses a process in which a vessel containing a small amount of a vaporizable liquid sterilant solution is attached to a lumen, and the sterilant vaporizes and flows directly into the lumen of the article as the pressure is reduced during the sterilization cycle. This system has the advantage that the water and hydrogen peroxide vapor are pulled through the lumen by the pressure differential that exists, increasing the sterilization rate for lumens, but it has the disadvantage that the vessel needs to be attached to each lumen to be sterilized. In addition, water is vaporized faster and precedes the hydrogen peroxide vapor into the lumen.

Brief Summary Text (16):
One aspect of the present invention relates to a method for sterilizing an interior of an article with a diffusion restricted area, such as an article having a lumen. The method includes the steps of contacting the interior of the article with a source of peroxide, and exposing the article to negative pressure for a time period sufficient to effect complete sterilization. In one embodiment, the source of peroxide comprises a liquid or condensed vapor. In another embodiment, the source of peroxide comprising a liquid comprises hydrogen peroxide or peracetic acid. In another embodiment, the source of peroxide comprising a condensed vapor comprises hydrogen peroxide or peracetic acid vapor. If the exposing step is conducted for 1 hour at 40.degree. C. and 10 torr, and the source of peroxide comprises 1 mg/L hydrogen peroxide, the diffusion restricted area preferably retains 0.17 mg/L or more hydrogen peroxide, or retains 17% or more of the hydrogen peroxide placed therein after the exposing step. In certain preferred embodiments, the diffusion-restricted area has the same or more diffusion restriction than provided by a lumen 27 cm in length and an internal diameter of 3 mm, or has the same or more diffusion restriction than provided by a lumen having a ratio of length to internal diameter greater than 50. The source of peroxide is preferably at a concentration of less than 25% by weight. The contacting step can be performed by delivery via a method such as injection, static soak, liquid flow-through, aerosol spray, condensation or physical placement. In a preferred embodiment, the diffusion-restricted area is a lumen at least 27 cm in length and having an internal diameter of no more than 3 mm, more preferably having an internal diameter of no more than 1 mm. The exposing step is preferably performed for 60 minutes or less, and is preferably performed at a pressure less than the vapor pressure of hydrogen peroxide. Thus, the preferred pressure range under conditions of the present invention is between 0 and 100 torr. In one particularly preferred embodiment, the pressure is approximately 10 torr and the exposing step is conducted at a temperature of approximately 23.degree. C. to approximately 28.degree. C. The exposing step can include the step of heating the article, such as by heating the chamber in which the exposing step occurs. The chamber can be heated to about 40.degree. C. to about 45.degree. C. Alternatively, the source of peroxide can be heated, such as to a temperature of about 40.degree. C. to about 45.degree. C. Optionally, the step of exposing the device to a plasma can be conducted during the step of exposing the device to negative pressure. In one embodiment employing exposure to plasma, the method is performed within a first chamber and the plasma is generated in a second, separate chamber. This embodiment further comprises the step of flowing the plasma into the first chamber. Advantageously, the contacting and/or exposing steps of the method can be repeated one or more times.

Brief Summary Text (17):
Another aspect of the present invention relates to a method for sterilizing an interior and an exterior of an article. This method includes the following steps: contacting the article with a source of peroxide; and placing the article in a diffusion-restricted environment. The contacting and placing steps can be performed in either order. These steps are followed by exposing the diffusion-restricted environment to negative pressure for a time period sufficient to effect complete sterilization. The contacting step can be performed both before and after the placing step. If the exposing step is conducted at 40.degree. C. and 10 torr, and a source of peroxide comprising 1 mg/L of hydrogen peroxide is introduced, the diffusion restricted environment preferably retains 0.17 mg/L or more hydrogen peroxide after the exposing step, or retains 17% or more of the hydrogen peroxide placed therein after the exposing step. The exposing step can include the step of heating the article, such as by heating the chamber in which the exposing step occurs or by heating the source of peroxide. In certain preferred embodiments, the diffusion-restricted environment has the same or more diffusion restriction than provided by a single entry/exit port of 9 mm or less in internal

diameter and 1 cm or greater in length, or is sufficiently diffusion restricted to completely sterilize a stainless steel blade within a 2.2 cm by 60 cm glass tube having a rubber stopper with a 1 mm by 50 cm stainless steel exit tube therein at a vacuum of 10 torr for one hour at 40.degree. C. In one embodiment, the source of peroxide comprises a liquid or condensed vapor. In another embodiment, the source of peroxide comprising a liquid comprises hydrogen peroxide or peracetic acid. In another embodiment, the source of peroxide comprising a condensed vapor comprises hydrogen peroxide or peracetic acid vapor. The contacting step can be by delivery via a method such as injection, static soak, liquid flow-through, aerosol spray, condensation or physical placement. Plasma can also be used during the step of exposing the lumen to negative pressure. If plasma is used, the method can be performed within a sealed chamber and the plasma generated within the container. Thus, the method can be performed within a first chamber and the plasma generated in a second, separate chamber and the plasma flowed into the first chamber. The diffusion-restricted container can have at least one exit tube, such as one that is at least 1.0 cm in length and has an internal diameter of 9 mm or less. The exit tube can also include a filter. In a preferred embodiment, the filter is sufficient to prevent entry of bacteria from the environment into the container. The source of peroxide can be used at a concentration of less than 25% by weight. The exposing step is preferably performed for 60 minutes or less. The method can be conducted along with the step of heating the article during the exposing step. Thus, the exposing step can be conducted within a chamber, and the chamber heated during the exposing step. The exposing step can be conducted at a negative pressure between 0 and 100 Torr. Advantageously, the various steps of this method can also be repeated one or more times.

Brief Summary Text (18):
Still one more aspect of the invention relates to a method for making a sterilized article within a diffusion-restricted container. This method includes contacting the article with a source of peroxide, and placing the article in the diffusion-restricted container in either order. If the initial contacting step precedes the placing step, the contacting step can be repeated after the placing step. These steps are followed by exposing the diffusion-restricted container to negative pressure for a time period sufficient to effect complete sterilization of the article. The container used in this aspect of the invention has at least one exit tube. The exit tube preferably has a filter therein which is preferably sufficient to prevent entry of bacteria into the container. The exit tube is at least 1.0 cm in length and/or has an internal diameter of 9 mm or less. Advantageously, the exposing step, the contacting step, or the entire method can be repeated one or more times. In a preferred embodiment, the contacting step comprises delivery via injection, static soak, liquid flow-through, aerosol spray, condensation or physical placement. The container can be exposed to a plasma during the step of exposing the container to negative pressure. In one embodiment, the method is performed within a sealed chamber and the plasma is generated within the chamber. The exposing step is preferably performed for 60 minutes or less and/or at a pressure between 0 and 100 Torr. The container can be heated during the exposing step, or the source of peroxide heated prior to the contacting step. The invention also includes the sterilized article within a diffusion-restricted container produced by the method of this aspect. In one embodiment, the source of peroxide comprises a liquid or condensed vapor. In another embodiment, the source of peroxide comprising a liquid comprises hydrogen peroxide or peracetic acid. In another embodiment, the source of peroxide comprising a condensed vapor comprises hydrogen peroxide or acetic acid vapor.

Brief Summary Text (19):
Still one more aspect of the invention relates to a method for making a sterilized article within a diffusion-restricted container. This method includes placing the article in the diffusion-restricted container and contacting the container with a source of peroxide, in either order. These steps are followed by exposing the diffusion-restricted container to negative pressure for a time period sufficient to effect complete sterilization of the article. The container used in this aspect of the invention has at least one communication port comprising an exit tube or air and vapor permeable window. The exit tube preferably has a filter therein which is preferably sufficient to prevent entry of bacteria into the container. The exit tube is at least 1.0 cm in length and/or has an internal diameter of 9 mm or less. The communication port is preferably connected through a connector to the article to be sterilized, so that sterilant vapor may flow through the article and out of the container. The connector is preferably tubing or an adaptor which can be attached to a lumen of said article, or an enclosure which contains a portion of the article with the lumen. In one embodiment, the exit tube is additionally connected to a valve outside the container and the valve is connected with a vacuum source. In one embodiment, the communication port comprising a window is impermeable to microorganisms. Advantageously, the exposing

step, the contacting step, or the entire method can be repeated one or more times. In a preferred embodiment, the contacting step comprises delivery via injection, static soak, liquid flow-through, aerosol spray, condensation or physical placement. The container can be exposed to a plasma during the step of exposing the container to negative pressure. In one embodiment, the method is performed within a sealed chamber and the plasma is generated within the chamber. The exposing step is preferably performed for 60 minutes or less and/or at a pressure between 0 and 100 Torr. The container can be heated during the exposing step, or the source of peroxide heated prior to the contacting step. The invention also includes the sterilized article within a diffusion-restricted container produced by the method of this aspect. In one embodiment, the source of peroxide comprises a liquid, a solid or condensed vapor. In another embodiment, the source of peroxide comprising a liquid comprises hydrogen peroxide or peracetic acid. In another embodiment, the source of peroxide comprising a solid comprises a urea peroxide complex or sodium pyrophosphate peroxide complex or like complex. In another embodiment, the source of peroxide comprising a condensed vapor comprises hydrogen peroxide or acetic acid vapor.

Detailed Description Text (2):
Sterilizing the inside of lumened devices has always posed a challenge to sterilization systems. Achieving rapid sterilization of lumened devices or other diffusion restricted articles at low temperatures and low concentrations of sterilant represents an even greater challenge. In the present invention, the shortcomings of the prior art sterilization systems are overcome by pre-treating or contacting articles to be sterilized with a source of peroxide prior to exposure to a vacuum, or optionally, plasma. Alternatively, a diffusion-restricted environment containing articles to be sterilized can be contacted with a source of peroxide prior to exposure to a vacuum. The source of peroxide comprises a liquid or condensed vapor in the case wherein an article is contacted. In the case wherein a diffusion-restricted environment is contacted, the source of peroxide additionally comprises a solid. The liquid comprises aqueous solutions of hydrogen peroxide or peracetic acid. The solid comprises a urea peroxide complex, or sodium pyrophosphate peroxide complex or like peroxide complex. The vapor comprises hydrogen peroxide or peracetic acid vapor. The preferred method of the present invention utilizes aqueous hydrogen peroxide as the source of peroxide to contact an article to be sterilized. The methods of the present invention provide for the rapid sterilization of lumened and non-lumened articles under conditions that will not damage the articles nor leave toxic residues on the sterile articles.

Detailed Description Text (3):
In the method of the present invention, the source of the peroxide is delivered into direct contact with the article to be sterilized or with the diffusion-restricted environment containing the article to be sterilized. In the case of a lumened device, the source of peroxide may be delivered directly into the lumen. In the case of an article having an area where diffusion of vapor is restricted, the source of peroxide may be delivered to the interior of the diffusion restricted area. For articles which are not diffusion-restricted, the source of peroxide can be introduced anywhere into the diffusion-restricted environment. The source of peroxide is delivered into the lumen or into contact with the article to be sterilized or into contact with the diffusion-restricted environment containing the article to be sterilized through means such as direct delivery or physical placement, a static soaking process, a liquid flow-through process, by aerosol spray or by condensation of a vapor. Physical placement also includes placement of a reservoir containing the source of peroxide. In the preferred method of the present invention, the aqueous solutions of hydrogen peroxide can be relatively dilute, e.g., as low as 1-6% or lower by weight, since sterilization is not achieved through contact with the hydrogen peroxide solution, but rather, is achieved at low temperatures and in short periods of time upon exposure to hydrogen peroxide vapor under vacuum or vacuum combined with plasma. The method of the present invention is particularly effective with articles having inaccessible or hard-to-reach places. Such articles include long, narrow lumens, hinges, and other articles having spaces where diffusion of vapors is restricted.

Detailed Description Text (18):
To determine the efficacy of the preferred sterilization method of the present invention, preliminary tests were first performed to evaluate the effect of dilute hydrogen peroxide solutions on contaminated surfaces in an open, non-diffusion restricted environment. These tests are described below in Example 1.

Detailed Description Text (20):
To evaluate the sterilization efficacy of dilute hydrogen peroxide solution alone, a biological challenge consisting of 2.5.times.10.sup.6 Bacillus stearothermophilus

spores on a stainless steel scalpel blade was used. Inoculated blades were submerged in 40 ml of hydrogen peroxide solution in a 100 ml beaker. Four different concentrations of hydrogen peroxide solution were used: 3%, 6%, 9% and 12% by weight. The blades were allowed to soak in the peroxide solutions for various time periods. The blades were then removed from the solution and tested for sterility. The results of this testing are listed in Table 1 as a ratio of the number of inoculated blades which remain contaminated after treatment over the number of inoculated blades tested.

Detailed Description Text (21):
Complete sterilization was not effected until after the blades had been soaked in 12% hydrogen peroxide solution for at least 90 minutes. Moreover, none of the blades tested were sterilized after 2 hours in .sup.6 % hydrogen peroxide solution. It is clear from these data that contact with dilute hydrogen peroxide solution alone is ineffective at providing sterilization, unless extended soak times and concentrated solutions are used.

Detailed Description Text (22):
Testing was next performed to evaluate the effect on the sterilization of long, narrow lumens of a pretreatment step in which the lumens to be sterilized are exposed to hydrogen peroxide solution prior to exposure to a vacuum. The testing evaluated the efficacy of hydrogen peroxide vapor sterilization inside the lumens. The testing is detailed below in Example 2.

Detailed Description Text (24):
A biological challenge consisting of 1.9.times.10.sup.6 B. stearothermophilus spores on a stainless steel scalpel blade was used. Some inoculated blades were pre-treated with a solution of aqueous hydrogen peroxide. Other inoculated blades, designated control blades, did not receive pretreatment with hydrogen peroxide. The pretreatment consisted of 5 minutes of static soaking in peroxide solution. The pre-treated blades were blotted dry, and each blade was then placed inside a stainless steel lumen, 3 mm internal diameter (ID).times.50 cm length. The lumen had a center piece of 1.3 cm ID and 5 cm length. The pre-treated blade was placed inside this center piece, and additional hydrogen peroxide solution was added into the center piece in various amounts. Control blades were handled identically, except that they did not receive pretreatment with hydrogen peroxide solution. The lumens were placed in a vacuum chamber, and the chamber was evacuated to 1 Torr and held there for 15 minutes, during which time the temperature increased from approximately 23.degree. C. to approximately 28.degree. C. Following exposure to the vacuum, the chamber was vented and the blades were removed from the chamber and tested for sterility. The results were as follows:

Detailed Description Text (28):
A biological challenge consisting of 1.9.times.10.sup.6 B. stearothermophilus spores on a stainless steel scalpel blade was used. Test A in Table 3 below consisted of the inoculated blades being pretreated with a solution of 3% aqueous hydrogen peroxide. The pretreatment consisted of 5 minutes of static soaking in the peroxide solution. The pretreated blades were blotted dry, then placed into the center piece of a stainless steel lumen which varied in size, together with 10 .mu.l of 3% hydrogen peroxide solution. The center piece was 1.3 cm ID and 5 cm length. Test B in Table 3 below consisted of identically inoculated control blades which did not receive pretreatment with hydrogen peroxide. Each inoculated control blade was placed directly into the center piece of a stainless steel lumen together with 10 .mu.l of 3% hydrogen peroxide solution. The center piece had dimensions identical to those in Test A. Lumens of various dimensions were used to evaluate the effect on sterilization of lumen internal diameter and length. The lumens were placed in a vacuum chamber, and the chamber was evacuated to 1 Torr for 15 minutes. During this 15 minutes of the sterilization cycle, the temperature increased from approximately 23.degree. C. to approximately 28.degree. C. Following exposure to the vacuum, the chamber was vented and the blades were removed from the chamber and tested for sterility. The results are reported in Table 3, where "L/D Ratio" indicates the ratio of length to internal diameter.

Detailed Description Text (29):
All lumens having a L/D ratio greater than 50 which were tested under the conditions of Test A of Example 3 were sufficiently diffusion-restricted to be sterilized in this system. Thus, it is believed that other lumens having an L/D ratio greater than 50 should also provide a sufficient level of diffusion-restriction for sterilization in accordance with the present invention. This testing shows that, in direct contrast to prior art methods, sterility through diffusion of hydrogen peroxide vapor from inside the article to outside the article is easier to achieve in longer, narrower lumens than in shorter, wider lumens. This is believed to be due to the larger lumens allowing too

much of the hydrogen peroxide vapor to diffuse out of the inside of the lumen during the sterilization process. Thus, the vapor does not contact the internal surfaces for a period of time sufficient or at a concentration sufficient to effect sterilization.

Detailed Description Text (30):
As discussed above, prior art methods of hydrogen peroxide vapor sterilization of lumens are generally limited to use on relatively short and wide lumens. In contrast to these prior art methods, the method of the present invention is effective on the interior of long, narrow lumens, including those longer than 27 cm in length and/or having an internal diameter of less than 3 mm.

Detailed Description Text (31):
To determine whether the ability of the sterilant vapor to diffuse within the system is a critical factor in achieving sterility, additional testing was performed to compare diffusion restricted and open, non-diffusion restricted systems. A non-diffusion restricted system is one in which the diffusion of vapors in and around the article is not restricted by narrow openings, long, narrow lumens, or the like. As used herein, "diffusion-restricted" refers to any one or more of the following properties: (1) the ability of an article placed within the sterilization system of the present invention to retain 0.17 mg/L or more hydrogen peroxide solution after one hour at 40.degree. C. and 10 torr; (2) having the same or more diffusion restriction than provided by a single entry/exit port of 9 mm or less in internal diameter and 1 cm or greater in length; (3) having the same or more diffusion restriction than provided by a lumen 27 cm in length and having an internal diameter of 3 mm; (4) having the same or more diffusion restriction than provided by a lumen having a ratio of length to internal diameter greater than 50; (5) the ability of an article placed within the sterilization system of the present invention to retain 17% or more of the hydrogen peroxide solution placed therein after one hour at 40.degree. C. and 10 torr; or (6) being sufficiently diffusion-restricted to completely sterilize a stainless steel blade within a 2.2 cm by 60 cm glass tube having a rubber stopper with a 1 mm by 50 cm stainless steel exit tube therein at a vacuum of 10 torr for one hour at 40.degree. C. in accordance with the present invention. It is acknowledged that characteristics (1) and (5) will vary depending on the initial concentration of hydrogen peroxide placed into the article; however, this can be readily determined by one having ordinary skill in the art.

Detailed Description Text (32):
As discussed in the Background of the Invention, articles having diffusion restricted areas are difficult to sterilize using known methods of hydrogen peroxide vapor sterilization, since these methods are dependent upon the diffusion of peroxide vapors from outside the article to the interior of the article. Testing performed to evaluate the importance of sterilant vapor diffusion is described in Example 4.

Detailed Description Text (34):
Hydrogen peroxide vapor sterilization was tested in both open and diffusion restricted systems. The open system consisted of stainless steel lumens having internal diameters of 1, 3, and 6 mm, and lengths of 15, 27, 40 and 50 cm. Stainless steel scalpel blades were inoculated with 1.9.times.10.sup.6 B. stearothermophilus spores, and the blades placed in the center piece of the lumen together with 10 .mu.l of 3% hydrogen peroxide solution. The dimensions of the center piece were 1.3 cm ID, 5 cm length and 6.6 cc volume.

Detailed Description Text (35):
The diffusion restricted system is illustrated in FIG. 1. Identically inoculated scalpel blades 5 were placed within the center pieces 10 of lumens 15 having dimensions identical to those described above. Ten .mu.l of 3% hydrogen peroxide solution was also added to the center piece 10 of the lumen 15. The lumen 15 was then placed within a 2.2 cm.times.60 cm glass tube 20. The tube 20 was closed at one end, and the open end was plugged with a rubber stopper 25 having a 1 mm.times.10 cm stainless steel tube 30 inserted through the stopper 25. Thus, gases entering or exiting the glass tube 20 could pass only through this 1 mm 20.times.10 cm opening.

Detailed Description Text (37):
Under the test conditions of Example 4, sterilization was not achieved in the shorter, wider lumens in the open system without pre-treatment with hydrogen peroxide. Pre-treatment, and other test conditions, such as higher peroxide concentration or longer treatment time, would likely allow sterilization of the 27 cm.times.3 mm lumen, which has an L/D ratio greater than 50. In the diffusion restricted system, the blades were sterilized in all sizes of lumens, using a 3% hydrogen peroxide solution.

Detailed Description Text (38):
These results indicate that providing a source of hydrogen peroxide within a diffusion restricted environment allows for complete sterilization within the system. It is the restriction of vapor diffusion in the system, not the length or internal diameter of the lumen per se that determines the efficacy of the hydrogen peroxide vapor sterilization. Again, however, these data show that, unlike the prior art methods of hydrogen peroxide vapor sterilization of lumens, the method of the present invention is effective even on non-diffusion-restricted articles when placed into a diffusion-restricted environment.

Detailed Description Text (41):
A stainless steel scalpel blade 5 was placed within a 2.2 cm.times.60 cm glass tube 20 which was closed at one end, as illustrated in FIG. 2. Each blade 5 had been inoculated with 1.9.times.10.sup.6 B. stearothermophilus spores. For some of the testing, the glass tube 20 was left open at one end, providing an open system. To create a diffusion restricted environment, the open end of the glass tube 20 was sealed with a rubber stopper 25 having a 1 mm.times.10 cm stainless steel tube 30 through its center. In both the open and diffusion restricted systems, hydrogen peroxide solution at a concentration of either 3% or 6% was added to the glass tube 20 in amounts of 50, 100, 150 or 200 .mu.l, together with the inoculated blade 5. The tube 20 was placed in a vacuum chamber, and the chamber evacuated to 1 Torr for 15 minutes, during which time the temperature increased from approximately 23.degree. C. to approximately 28.degree. C. The diffusion restricted system only was also tested at 1 Torr for 30 minutes, during which time the temperature increased from approximately 23.degree. C. to approximately 33.degree. C. The vacuum chamber was then vented, and the blades 5 removed from the tube 20 and tested for sterility. The results are listed in Table 5 below.

Detailed Description Text (42):
These results show that the addition of hydrogen peroxide solution, followed by exposure to vacuum, is ineffective for achieving rapid sterilization in an open system. Identical treatment in a diffusion restricted system, by comparison, results in complete sterilization, except at the very weakest concentration of hydrogen peroxide solution in an amount of only 50 .mu.l. Sterilization can be effected, however, by increasing the exposure to the vacuum.

Detailed Description Text (43):
Thus, the method of the present invention, wherein small amounts of hydrogen peroxide solution are delivered to the article to be sterilized prior to exposure to a vacuum, is an effective method of sterilization. The method does not depend on the diffusion of sterilant vapor into the article being sterilized. Rather, the hydrogen peroxide vapor is created by the vacuum within the system. This vapor is prevented from leaving the system too quickly, because the diffusion of the sterilant vapor from the inside of the article to the outside of the article is slowed. In a diffusion restricted environment, the vapor therefore contacts the article to be sterilized for a period of time sufficient to effect complete sterilization. In addition, unlike the prior art methods where the water in the peroxide solution is vaporized first and becomes a barrier to the penetration of the peroxide vapor, the method of the present invention removes any water from the system first, thereby concentrating the hydrogen peroxide vapor remaining in the system. More importantly, in the preferred method of the present invention, the diffusion of vapor is from the inside to outside rather than outside to inside as in the prior art. As a result, diffusion-restriction in the present invention serves to increase the effectiveness of sterilization rather than to decrease the effectiveness, as in the prior art.

Detailed Description Text (46):
A stainless steel scalpel blade 5 was placed within a 2.2 cm.times.60 cm glass tube 20 which was closed at one end, as shown in FIG. 2. Each blade 5 had been inoculated with 1.9.times.10.sup.6 B. stearothermophilus spores. To create a diffusion restricted environment, the open end of the glass tube 20 was sealed with a rubber stopper 25 having a 1 mm.times.10 cm stainless steel tube 30 through its center. Hydrogen peroxide solution at a concentration of 3% was added to the glass tube 20 in amounts of 50, 100, 150 or 200 .mu.l, together with the inoculated blade 5. The tube 20 was placed in a vacuum chamber, and subjected to various pressures for 15 minutes, during which time the temperature increased from approximately 23.degree. C. to approximately 28.degree. C. In a further experiment to determine the effect of increased temperature on the system, the tube 20 was first heated to 45.degree. C., then subjected to 50 Torr pressure for 15 minutes. The results were as follows.

Detailed Description Text (47):
These data show that sterilization can be achieved in diffusion restricted environments at pressures up to about 25 Torr at 28.degree. C. At pressures of 30 Torr and higher, sterilization was not achieved; this is believed to be due to the fact that the vapor pressure of hydrogen peroxide at 28.degree. C. is approximately 28 Torr. Thus, at higher pressures, the liquid hydrogen peroxide inside the glass tube was not vaporizing. This was confirmed by the testing done at 50 Torr pressure at 45.degree. C., wherein sterilization was achieved. The vapor pressure of hydrogen peroxide is increased at 45.degree. C., thus, the hydrogen peroxide was vaporized at 50 Torr, effectively sterilizing the blade placed inside the tube.

Detailed Description Text (48):
Accordingly, in order to achieve sterilization using the method of the present invention employing an aqueous solution of hydrogen peroxide, the temperature and pressure within the vacuum chamber should be such that vaporization of the aqueous hydrogen peroxide solution is achieved, i.e. the system should preferably be operated below the vapor pressure of the hydrogen peroxide. The pressure needs to be below the vapor pressure of hydrogen peroxide, such that the hydrogen peroxide solution present in the system is vaporized and diffuses from the interior of the diffusion restricted environment to the outside. Alternatively, the hydrogen peroxide can be vaporized locally where the system remains above the vapor pressure by introducing energy to the site of the peroxide, such as through microwaves, radio waves, or other energy sources.

Detailed Description Text (51):
A stainless steel scalpel blade 5 was placed within a 2.2 cm.times.60 cm glass tube 20 which was closed at one end, as illustrated in FIG. 2. Each blade 5 had been inoculated with 1.9.times.10.sup.6 B. stearothermophilus spores. To create a diffusion restricted environment, the open end of the glass tube 20 was sealed with a rubber stopper 25 having a 1 mm.times.10 cm stainless steel tube 30 through its center. Hydrogen peroxide solution at a concentration of 3% was added to the glass tube 20 in amounts of 50, 100, 150 or 200 .mu.l together with the inoculated blade 5. The tube 20 was placed in a vacuum chamber, and the chamber evacuated to 5 Torr. To vary the pressure within the chamber, the valve to the vacuum pump was closed, such that the pressure within the chamber rose from 5 Torr to 6.15 Torr after 15 minutes, during which time the temperature increased from approximately 23.degree. C. to approximately 28.degree. C. In a second test, the tube 20 was placed in the chamber and the chamber was evacuated to 50 Torr. The temperature of the glass tube 20 was increased to 45.degree. C. after the evacuation of the chamber was complete. The tube 20 was treated for 15 minutes. The results of these tests are reported below.

Detailed Description Text (52):
These results show that maintaining a constant pressure or temperature is not required in the diffusion restricted environment to effect sterilization. Under the conditions tested, the hydrogen peroxide is vaporized and kept in contact with the device to be sterilized for a time sufficient to effect complete sterilization.

Detailed Description Text (53):
The preferred method of the present invention relies on the delivery of liquid hydrogen peroxide to the article to be sterilized prior to vacuum or plasma treatment. The following testing was performed to determine the effect of the location of the delivery of the hydrogen peroxide within the diffusion restricted environment.

Detailed Description Text (55):
A stainless steel scalpel blade 5 was inoculated with 1.9.times.10.sup.6 B. stearothermophilus spores, and the blade 5 placed in the center piece 10 of a lumen 15 as illustrated in FIG. 1. The dimensions of the center piece 10 were 1.3 cm ID, 5 cm length and 6.6 cc volume, while the lumen itself varied in size, having an ID of 1, 3 or 6 mm, and a length of 15, 27, 40 or 50 cm. The lumen 15 was placed within a 2.2 cm.times.60 cm glass tube 20. The tube 20 was closed at one end, and the open end was plugged with a rubber stopper 25 having a 1 mm.times.10 cm stainless steel tube 30 placed through the stopper 25. Thus, gases entering or exiting the glass tube 20 could pass only through this 1 mm.times.10 cm opening. 10 .mu.l of 3% hydrogen peroxide solution was placed inside the lumen 15, or 100 .mu.l of 3% hydrogen peroxide solution was placed inside the glass tube 20, but outside the stainless steel lumen 15. The glass tube 20 was then placed in a vacuum chamber, which was sealed and evacuated to 1 Torr for 15 minutes, during which time the temperature increased from approximately 23.degree. C. to approximately 28.degree. C. Results of this testing are as follows.

Detailed Description Text (56):
These data show that, under the test conditions of Example 8, sterilization did not occur within the inner lumen when the hydrogen peroxide solution was placed outside the lumen in a diffusion restricted environment, but that complete sterilization was effected when the hydrogen peroxide solution was placed inside all of the lumens in a diffusion restricted environment. When the hydrogen peroxide vapor must diffuse from outside to inside, the sterilant vapor cannot enter the inner lumen in a diffusion restricted environment unless the lumen is sufficiently large. Thus, when the hydrogen peroxide solution was placed outside the lumen, only the shortest, widest lumens allowed sufficient vapor penetration to allow sterilization inside the lumen. These data confirm that prior art methods which require diffusion of sterilant vapor from outside the article to the interior article cannot achieve sterilization in diffusion restricted environments under these conditions. In contrast, under the same conditions except where the hydrogen peroxide was placed inside the article, allowing hydrogen peroxide to diffuse from inside to outside, complete sterilization occurred with much lower amounts of hydrogen peroxide.

Detailed Description Text (59):
A stainless steel scalpel blade 5 was inoculated with 1.9.times.10.sup.6 B. stearothermophilus spores, and placed in a 2.2 cm.times.60 cm glass tube 20 as illustrated in FIG. 2. The tube 20 was closed at one end, and the open end was plugged with a rubber stopper 25. Stainless steel tubing 30 of various dimensions was inserted through the stopper 25. Thus, gases entering or exiting the glass tube 20 could pass only through the opening in the tubing 30, which varied from 1 mm to 6 mm in diameter. Three percent hydrogen peroxide solution in volumes ranging from 50 .mu.L to 200 .mu.L was also placed inside the glass tube 20. The glass tube 20 was then placed in a vacuum chamber, which was sealed and evacuated to 5 Torr for 15 minutes, during which time the temperature increased from approximately 23.degree. C. to approximately 28.degree. C. In addition, three lumens were tested at 10 Torr for 15 minutes with 3% hydrogen peroxide. The results of this testing are listed below in Table 9.

Detailed Description Text (60):
Complete sterilization was achieved in the majority of the environments tested. Sterilization could not be achieved at 5 torr using the shortest length of stainless steel tubing and only 50 .mu.l hydrogen peroxide solution. Greater volumes of hydrogen peroxide must be used in these systems.

Detailed Description Text (61):
These data also confirm that the vacuum pressure affects sterilization efficacy, since the container with the shortest and widest exit tube could provide sterilization at 10 Torr, but not at 5 Torr. At too low pressures (such as pressures below 5 Torr in the conditions tested) however, it appears that the hydrogen peroxide vapor is pulled from the interior of the article being sterilized too quickly, resulting in an insufficient amount of hydrogen peroxide vapor being allowed to contact the interior of the device to effect sterilization. It would appear that although a pressure of 5 torr produces acceptable results, a pressure of approximately 10 Torr is better under the conditions tested.

Detailed Description Text (64):
For this testing, a diffusion restricted system was tested. 1.2.times.10.sup.6 B. stearothermophilus spores were inoculated onto non-woven polypropylene pieces. As illustrated in FIG. 1, the inoculated pieces 5 were placed inside the center piece 10 of a plastic lumen 15, together with 10 .mu.l of 3% hydrogen peroxide solution. The center piece 10 was made of Teflon.TM. and had dimensions of 1.3 cm .times.5 cm. The lumen 15 varied from 1 mm to 6 mm ID, and 15 cm to 50 cm in length. Teflon.TM. was used for the 1 mm lumen, polyethylene was used for the 3 mm and 6 mm lumen. The lumen 15 was then placed within a 2.2 cm.times.60 cm glass tube 20. The glass tube 20 was closed on one end, and the open end was sealed with a rubber stopper 25 having a 1 mm.times.10 cm piece of PTFE tubing 30 through it. The glass tube 20 was placed in the vacuum chamber and treated for 15 minutes at 1 Torr, during which time the temperature increased from approximately 23.degree. C. to approximately 28.degree. C. The results of this testing are set forth below.

Detailed Description Text (66):
To further confirm this, 2.1.times.10.sup.6 B. stearothermophilus spores were inoculated on stainless steel blades, and 1.2.times.10.sup.6 B. stearothermophilus spores were inoculated onto non-woven polypropylene pieces. As shown in FIG. 2, the blades 5 or non-woven polypropylene pieces 5 were placed inside a 2.2 cm.times.60 cm glass tube 20 together with 50 .mu.l of 3% hydrogen peroxide solution. One end of the

tube was closed, and the open end was sealed with a rubber stopper 25 having either a 1 mm.times.10 cm stainless steel tube 30 therein, or a 1 mm.times.10 cm piece of Teflon.TM. tubing 30 therein. The glass tube 20 was placed inside a vacuum chamber and treated for 15 minutes at 5 Torr, during which time the temperature increased from approximately 23.degree. C. to approximately 28.degree. C. The results are as follows.

Detailed Description Text (67):
Thus, all four combinations of metal and plastic provide for effective hydrogen peroxide vapor sterilization in a diffusion restricted environment. This testing confirms that the method of the present invention is an effective sterilization method for diffusion restricted articles, and can be used on a wide variety of such articles, regardless of the materials used to form them.

Detailed Description Text (70):
Stainless steel blades were inoculated with 2.1.times.10.sup.6 B. stearothermophilus spores. The blades 5 were placed inside a 2.2 cm.times.60 cm glass tube 20 as illustrated in FIG. 2, along with various amounts of 3% hydrogen peroxide solution. The glass tube 20 was placed in a vacuum chamber and subjected to different pressures and different temperatures for various periods of time. During the sterilization cycles reported in Table 11A, the temperature increased from approximately 23.degree. C. to the temperatures indicated. In the experiments reported in Table 11B, the chamber was heated to approximately 45.degree. C. In an alternative embodiment, rather than heating the chamber, the temperature of the peroxide solution itself can be heated. In the experiments reported in Table 11C, the temperature increased from approximately 23.degree. C. to approximately 28.degree. C. during the 15 minute period of exposure to vacuum.

Detailed Description Text (71):
Under the test conditions of Example 11, large volumes of hydrogen peroxide solution were ineffective at achieving sterilization when vacuum was applied for only very short periods of time. This is believed to be at least partially because water vaporizes more quickly than hydrogen peroxide. Thus, the water present in the aqueous solution will vaporize first, and more time is needed to vaporize the hydrogen peroxide. This also explains why the larger volumes of hydrogen peroxide solution were effective at achieving sterilization at higher temperatures; the vaporization of the hydrogen peroxide occurs sooner at higher temperatures. Thus, when more water is present in the system, either higher temperatures or more time is required to achieve sterilization.

Detailed Description Text (72):
Again, it would appear from these data that slightly higher pressures, i.e. 10 Torr, achieve more effective sterilization under these conditions. This is believed to be because at higher pressures, more hydrogen peroxide vapor is retained inside the system. At too low a pressure, the hydrogen peroxide vapor is pulled out of the system too quickly.

Detailed Description Text (75):
Various concentrations of peroxide were used in a system substantially as described in connection with FIG. 2. In this system, the exit tube 35 was a stainless steel tube having a length of 50 cm and an internal diameter of 1 mm. A stainless steel blade inoculated with 1.9.times.10.sup.6 spores of B. stearothermophilus was placed within the container which was a 2.2 cm.times.60 cm glass tube. Various amounts of 3% hydrogen peroxide were introduced into the container. The container was placed in a vacuum chamber of 173 liters, and the pressure reduced to 10 Torr for a period of one hour, during which time the temperature increased from approximately23.degree. C. to approximately 40.degree. C. Sporicidal activity was evaluated at each concentration of peroxide. In addition, the amount of peroxide remaining in the container after the sterilization process was evaluated by standard titration techniques, whereby the peroxide was reacted with potassium iodide and titrated with sodium thiosulfate. Results are shown in Table 12 where "N/D" indicates not determined.

Detailed Description Text (76):
The results reported in Table 12 indicate that 1.0 mg/L of 3% liquid peroxide were required in the system tested to effect sterilization. Further, under the conditions tested, a concentration of 0.17 mg/L of peroxide remaining in the system was sufficient to provide complete sterilization. These data also show that the glass tube used in these experiments provided a sufficient level of diffusion restriction to retain 17% of the hydrogen peroxide placed therein.

Detailed Description Text (84):

A stainless steel blade was inoculated with 2.1.times.10.sup.6 B. stearothermophilus spores. The blade 5 was placed inside a 2.2 cm.times.60 cm glass tube 20 as shown in FIG. 3, together with various amounts of 3% hydrogen peroxide solution. One end of the tube was closed, and the open end was sealed with a rubber stopper 25 having a syringe filter 35 inserted therein. The glass tube 20 was placed inside a vacuum chamber and treated for 15 minutes at 5 Torr, during which time the temperature increased from approximately 23.degree. C. to approximately 28.degree. C. As a control, identically inoculated blades were placed inside 2.2 cm.times.60 cm glass tubes. The open end of the tubes was left open, no stopper or syringe filter was used. Thus, the diffusion of vapor from the interior of the tube was not restricted.

Detailed Description Text (86):
As is apparent from these results, certain brands of filters do not create a sufficiently diffusion restricted environment at 5 Torr pressure when only 50 .mu.L of hydrogen peroxide solution is placed in the system. Other brands of filters did provide sufficient diffusion restriction; these brands of filters had either longer lumens or smaller filter pore size. Using larger volumes of peroxide solution, 10 Torr pressure, or serial filters enhances the efficacy of the sterilization system. This is important, as filters, including ones made of Tyvek.TM., are often used in packaging of sterile articles to prevent recontamination with bacteria. These filters generally have a pore size of 1 .mu.m or less, or in the case of Tyvek.TM., create a tortuous path which bacteria cannot cross. In the present invention, filters can be used in combination with other packaging means to create a diffusion restricted environment to effect sterilization, and the sterile article can remain inside the packaging during storage prior to use; the filter will prevent re-contamination of the sterile article.

Detailed Description Text (92):
These results show that peracetic acid, in which hydrogen peroxide coexists, can also be used in the sterilization method of the present invention.

Detailed Description Text (93):
It was discovered that by delivering small amounts of hydrogen peroxide solution to an article to be sterilized prior to exposure to vacuum, sterilization could be effected at lower temperatures and in short periods of time. The following testing was performed to evaluate different methods of delivering hydrogen peroxide solution to the article to be sterilized. Further, the efficacy of vacuum treatment and plasma treatment following pretreatment with aqueous hydrogen peroxide were compared. The testing is described in Example 16 below.

Detailed Description Text (95):
In a first series of tests, stainless steel blades were inoculated with 2.5.times.10.sup.6 B. stearothermophilus spores. The blades were placed in the expanded center piece of a 3 mm.times.50 cm stainless steel lumen. The lumen was placed in a 1000 ml beaker containing 800 ml of hydrogen peroxide solution. The lumen was soaked for 5 minutes in 3% hydrogen peroxide solution. The number of surviving organisms following this initial soak was determined. The lumens were removed from the hydrogen peroxide solution and the outside blotted dry with paper towels. The inside of the lumens were dried by placing one end of the lumen into a flask and blowing with a three second burst of compressed air. The lumens were shaken, and the blowing and shaking repeated until no more solution was blown out. Subsequently, the lumen was placed in a sterilization chamber and exposed to either a vacuum of 0.5 Torr for 15 minutes, or plasma for 15 minutes at 0.5 Torr. After 15 minutes of vacuum, the temperature increased from approximately 23.degree. C. to approximately 28.degree. C. The results are set forth below in Table 16A.

Detailed Description Text (96):
A five minute soak in 3% hydrogen peroxide solution was an effective means for delivering the hydrogen peroxide into the lumen prior to vacuum or plasma treatment. As noted before, treatment with hydrogen peroxide solution only is ineffective to achieve sterilization using dilute solutions and short soak times. Delivery of hydrogen peroxide solution via static soaking is at least as effective a way to deliver the hydrogen peroxide as depositing small volumes directly into the lumen of the device.

Detailed Description Text (97):
Flow-through delivery of hydrogen peroxide was tested next. Here, stainless steel blades were inoculated with 2.5.times.10.sup.6 B. stearothermophilus spores. The blades were placed in the expanded center piece of a 3 mm.times.50 cm stainless steel lumen. Hydrogen peroxide solution at 3% concentration was delivered to the lumen at a flow rate of 0.1 L/min, using a peristaltic pump. The lumen was dried as described above.

Following pretreatment with hydrogen peroxide solution, the lumen was then placed in a sterilization chamber and exposed to either a vacuum of 0.5 Torr for 15 minutes, or plasma for 15 minutes at 0.5 Torr. The results are set forth below in Table 16B.

Detailed Description Text (98):
Delivery of the hydrogen peroxide solution via constant flow is also an effective way to deliver hydrogen peroxide to the system.

Detailed Description Text (99):
Finally, the effect of delivery of hydrogen peroxide by aerosol spray was tested. Stainless steel blades were inoculated with 2.5.times.10.sup.6 B. stearothermophilus spores. The inoculated blades were placed in the expanded center piece of a 3 mm .times.50 cm stainless steel lumen. Three percent hydrogen peroxide solution was delivered to the lumen via a 3 second aerosol spray. Aerosol spray rate was determined to be 0.04 L/min. After a 5 minute wait following pretreatment with hydrogen peroxide, the lumen was dried as described above and the lumen was then placed in a sterilization chamber and exposed to either a vacuum of 0.5 Torr for 15 minutes, or plasma for 15 minutes at 0.5 Torr. The results are set forth below in Table 16C.

Detailed Description Text (100):
Flow-through of hydrogen peroxide as either a liquid solution or aerosol can also be achieved by introducing increased pressure at the delivery end or decreased pressure at the exit end of the device to be treated.

Detailed Description Text (101):
It is evident from the data in Tables 16A-16C that all three methods of delivering hydrogen peroxide solution to the article to be sterilized provided for effective sterilization. Thus, it appears that a number of different methods of delivery can be used, as long as the hydrogen peroxide solution is present in the system prior to exposure to vacuum or plasma.

Detailed Description Text (102):
Finally, the efficacy of pretreatment with hydrogen peroxide prior to a sterilization cycle which combines exposure to hydrogen peroxide vapor, vacuum, and plasma was evaluated. The testing was as follows.

Detailed Description Text (104):
Stainless steel blades were inoculated with 2.5.times.10.sup.6 B. stearothermophilus spores. The blades were soaked in 3% hydrogen peroxide solution for either 1 or 5 minutes. The blades were then placed in the expanded center piece of a 3 mm .times.50 cm stainless steel lumen. The lumen was then placed in a sterilization chamber which was evacuated to approximately 0.5 Torr. The sterilization cycle consisted of 15 minutes of hydrogen peroxide vapor diffusion with a minimum of 6 mg/L hydrogen peroxide, followed by 15 minutes of plasma at 400 watts. Following the plasma treatment, the chamber was vented and the blades tested for sterility. The results are shown below.

Detailed Description Text (105):
Processing the lumens in a hydrogen peroxide vapor and plasma cycle alone left an average of 30 surviving organisms per blade. Pre-treating the blades by soaking in 3% hydrogen peroxide solution for 5 minutes alone left an average of 8.2.times.10.sup.5 surviving organisms per blade. Thus, under these particular test conditions, a combination of hydrogen peroxide vapor exposure and plasma exposure, which has been found to be effective for many articles, was ineffective in a diffusion restricted environment. However, by pre-treating the article to be sterilized with dilute hydrogen peroxide solution prior to exposure to hydrogen peroxide vapor and plasma, complete sterilization can be achieved.

Detailed Description Text (106):
While the invention has been described in connection with preferred liquid sterilant solutions containing hydrogen peroxide, it will be appreciated by those having ordinary skill in the art that equivalent sterilization methods can be adapted for other sources of peroxide sterilants. In an alternative embodiment, a sterilant having a vapor pressure lower than that of water or other solvent in which the sterilant may be provided is used. For such sterilants, it is only important that the vapor pressure be lower than that of the solvent within the temperature ranges contemplated herein. In yet other embodiments, a solid source of peroxide sterilant may be utilized. Such liquid and solid sterilants can be adapted for the techniques described herein with only minor adjustments made for the differences in vapor pressure between hydrogen

peroxide and such other sterilant, as can be readily determined by those having ordinary skill in the art. As long as the local vapor pressure at the site of the sterilant is below the vapor pressure of the sterilant, sterilization can be achieved substantially as described hereinabove.

Detailed Description Text (108):
Achieving rapid sterilization of lumened devices at low temperatures using low concentrations of sterilants has, until now, been exceedingly challenging. A superior method of sterilization has been discovered which overcomes the problems of the known methods. By pre-treating articles to be sterilized or a diffusion-restricted environment containing the articles with a source of peroxide such as an aqueous solution of hydrogen peroxide prior to exposure to a vacuum, rapid sterilization can be achieved at low temperatures, without damage to the articles, without leaving toxic residues behind, and without the need to attach special vessels. The method of the present invention is efficient, nonhazardous, and inexpensive as well.

Detailed Description Paragraph Table (2):
TABLE 2 Effect of Pretreatment and Hydrogen Peroxide Concentration on Sterilization of the Interior of Lumens Additional peroxide added Blades not pre-treated Blades pre-treated in into the center piece with peroxide peroxide solution (A) With 1% hydrogen peroxide solution and vacuum 10 .mu.L + + 20 .mu.L + + 30 .mu.L + + 40 .mu.L + + 50 .mu.L + + 100 .mu.L + - 150 .mu.L + - 200 .mu.L - - 250 .mu.L - - (B) With 3% hydrogen peroxide solution and vacuum 10 .mu.L - - 20 .mu.L - - 30 .mu.L - - 40 .mu.L - - 50 .mu.L - - 100 .mu.L - - 150 .mu.L - - 200 .mu.L - - 250 .mu.L - - (C) With 6% hydrogen peroxide solution and vacuum 10 .mu.L - - 20 .mu.L - - 30 .mu.L - - 40 .mu.L - - 50 .mu.L - -

Detailed Description Paragraph Table (4):
TABLE 4 Hydrogen Peroxide Vapor Sterilization in Open and Diffusion Restricted Systems Peroxide System amount Length 1 mm ID 3 mm ID 6 mm ID Open 10 .mu.L of 3% 50 cm - - - 40 cm - - - 27 cm - + + 15 cm - + + Diffusion 10 .mu.L of 3% 50 cm - - - Restricted 40 cm - - - Environment 27 cm - - - 15 cm - - -

Detailed Description Paragraph Table (5):
TABLE 5 Hydrogen Peroxide Vapor Sterilization in Open and Diffusion Restricted Systems 50 .mu.L 100 .mu.L 150 .mu.L 200 .mu.L Open System, 15 minutes vacuum at 1 Torr: 3% peroxide + + + + 6% peroxide + + + + Diffusion Restricted System, 15 minutes vacuum at 1 Torr: 3% peroxide + - - - 6% peroxide - - - - Diffusion Restricted System, 30 minutes vacuum at 1 Torr: 3% peroxide - - - -

Detailed Description Paragraph Table (6):
TABLE 6 Effect of Temperature and Pressure on a Diffusion Restricted System 50 .mu.L 100 .mu.L 150 .mu.L 200 .mu.L 15 minutes vacuum with 3% hydrogen peroxide solution: 1 torr pressure + - - - 5 torr pressure - - - - 10 torr pressure - - - - 15 torr pressure - - - - 20 torr pressure - - - - 25 torr pressure - - - - 30 torr pressure + + + + 35 torr pressure + + + + 40 torr pressure + + + + 45 torr pressure + + + + 50 torr pressure + + + + 15 minutes vacuum with 3% hydrogen peroxide at 45.degree. C.: 50 torr pressure - - - -

Detailed Description Paragraph Table (8):
TABLE 8 Effect of Hydrogen Peroxide Solution Placed Outside Inner Lumen Peroxide amount Length 1 mm ID 3 mm ID 6 mm ID 10 .mu.L of 3% 50 cm - - - in lumen 40 cm - - - 27 cm - - - 15 cm - - - 100 .mu.L of 3% 50 cm + + + in glass tube 40 cm + + + 27 cm + + + 15 cm + + -

Detailed Description Paragraph Table (9):
TABLE 9 Effects of Tubing Dimension and Vacuum Pressure on Sterilization 15 minutes vacuum at 5 Torr with 3% hydrogen peroxide SS tubing 50 .mu.L 100 .mu.L 150 .mu.L 200 .mu.L 1 mm .times. 10 cm - - - - 1 mm .times. 5 cm - - - - 1 mm .times. 2.5 cm + - - - 3 mm .times. 10 cm - - - - 3 mm .times. 5 cm - - - - 3 mm .times. 2.5 cm + - - - 6 mm .times. 10 cm - - - - 6 mm .times. 5 cm + - - - 6 mm .times. 2.5 cm + - - - 15 minutes vacuum at 10 Torr with 3% hydrogen peroxide SS tubing 50 .mu.L

_____ 1 mm .times. 2.5 cm - 3 mm .times. 2.5 cm - 6 mm .times. 2.5 cm - _____

Detailed Description Paragraph Table (17):
TABLE 14 _____ Sporicidal Activity of H.sub.2 O.sub.2 Solution with Vacuum in a Container Having a Syringe Filter 50 .mu.L 100 .mu.L 150 .mu.L 200 .mu.L _____ 15 minutes vacuum and 3% hydrogen peroxide: (a) Without syringe filter and stopper: 5 Torr + + + + 10 Torr + + + + (b) With MFS .TM. PTFE 25 mm syringe filter: (1) 0.2 .mu.m membrane filter 5 Torr + - - - 10 Torr - - - - (2) 0.5 .mu.m membrane filter 5 Torr + - - - 10 Torr - - - - _____ 50 .mu.L _____ (3) With 2 MFS .TM. filters together at 5 Torr pressure Two 0.2 .mu.m filters - Two 0.5 .mu.m filters - _____ 50 .mu.L 100 .mu.L 150 .mu.L 200 .mu.L _____ (c) With Nalgene .TM. PTFE 50 mm syringe filter: (1) 0.2 pm membrane filter 5 Torr - - - - 10 Torr - - - - (2) 0.45 .mu.m membrane filter 5 Torr - - - - 10 Torr - - - - _____ 50 .mu.L 100 .mu.L _____ (d) With Whatman Anotop .TM. 10 Plus syringe filter: (1) 0.02 .mu.m membrane filter 5 Torr - - 10 Torr - - (2) 0.1 .mu.m membrane filter 5 Torr - - 10 Torr - - (e) With Gelman Acrodisc .TM. CR PTFE syringe filter: (1) 0.2 .mu.m membrane filter 5 Torr + - 10 Torr - - (2) 0.45 .mu.m membrane filter 5 Torr + - 10 Torr - - (3) 1.0 .mu.m membrane filter 5 Torr + - 10 Torr - - _____

Detailed Description Paragraph Table (22):
TABLE 17 _____ Effects of H.sub.2 O.sub.2 Solution Soak on Sporicidal Activity in Stainless Steel Lumens Prior to a Hydrogen Peroxide Vapor and Plasma Cycle Sterility Test Results Conc. H.sub.2 O.sub.2 Soak Time Soak Alone Soak + Cycle _____ 3% 1 min 4/4 0/4 5 min 4/4 0/4 _____

CLAIMS:

1. A method for sterilizing an article within a container in a vacuum chamber, said method comprising:

(a) placing said article in said container, wherein said container is in fluid communication with the chamber through an exit tube having a length to internal diameter ratio greater than or equal to 1.1;

(b) contacting the interior of the container with a source of peroxide which releases hydrogen peroxide vapor, said placing and contacting steps being performed in either order;

(c) reducing the pressure of the chamber and container below the vapor pressure of hydrogen peroxide;

(d) generating hydrogen peroxide vapor in the container;

(e) diffusing said hydrogen peroxide vapor from the container through the exit tube into said vacuum chamber; and

(f) exposing said article to said hydrogen peroxide vapor for a time period sufficient to effect sterilization of said article.

5. The method of claim 1, further comprising the step of exposing said container to a plasma during the step of exposing the article to the hydrogen peroxide vapor.

12. The method of claim 11, wherein said liquid comprises hydrogen peroxide or peracetic acid.

14. The method of claim 11, wherein said condensed vapor comprises hydrogen peroxide or peracetic acid vapor.

20. A method for sterilizing a lumened article having an exterior surface and an interior surface within a container in a vacuum chamber, wherein said container is in fluid communication with the chamber through a communication port on the container, said method comprising:

(a) placing said article in said container, said article having a lumen with a length

to internal diameter ratio greater than or equal to 90;

(b) connecting the lumen of said article to the communication port through a connector;

(c) contacting the interior of the container with a source of peroxide which releases hydrogen peroxide vapor, said placing, connecting, and contacting steps being performed in any order;

(d) reducing the pressure of the chamber and container below the vapor pressure of hydrogen peroxide;

(e) generating said hydrogen peroxide vapor in the container;

(f) diffusing said hydrogen peroxide vapor from the container through the lumen, the connector, the communication port and into said vacuum chamber; and

(g) exposing said article to said hydrogen peroxide vapor to effect sterilization of the interior surface and the exterior surface of said article.

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DOCUMENT-IDENTIFIER: JP 01293871 A
TITLE: HYDROGEN PEROXIDE PLASMA STERILIZATION METHOD

Abstract Text (1):
PURPOSE: To achieve sterilization of the products by treating them with hydrogen peroxide without plasma, following which by treating them with plasma for removing the residual traces of hydrogen peroxide.

Abstract Text (2):
CONSTITUTION: The subjects, i.e., products to be sterilized are placed either into a vacuum vessel or plasma chamber, where the chamber pressure is then reduced down to about 0.05Torr. The aqueous solution of hydrogen peroxide is poured into the chamber, until the steam pressure of hydrogen peroxide become 0.5-10Torr. The concentration of hydrogen peroxide to be poured into the chamber is about 0.05-10mg/L (chamber capacity). The products to be sterilized are held in the chamber for about 5-30min. during whose period power enough to sterilize them is generated. After this pre-treatment, the products receive the plasma either in the pre-treatment chamber or another plasma chamber. The RF energy to generate the plasma may be either continuous or pulsed. The products are held in this plasma for 5-60min. and hydrogen peroxide is decomposed into the nontoxic products during this treatment.